LINK BETWEEN THE ENVIRONMENT AND CANCER: DOE'S RESEARCH EFFORTS

HEARING

BEFORE THE

SUBCOMMITTEE ON NATURAL RESOURCES,
AGRICULTURE RESEARCH AND ENVIRONMENT

OF THE

COMMITTEE ON
SCIENCE AND TECHNOLOGY
U.S. HOUSE OF REPRESENTATIVES

NINETY-EIGHTH CONGRESS

FIRST SESSION

MARCH 3, 1983

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LINK BETWEEN THE ENVIRONMENT AND CANCER: DOE'S RESEARCH EFFORTS

THURSDAY, MARCH 3, 1983

House of Representatives,
Committee on Science and Technology,
Subcommittee on Natural Resources,
Agriculture Research and Environment,
Washington, D.C.

The subcommittee met, pursuant to notice, at 2:35 p.m., in room 2318, Rayburn House Office Building, Hon. James H. Scheuer (chairman of the subcommittee) presiding.

Present: Representatives Scheuer, Andrews, Torricelli, Harkin, MacKay, McGrath, and Schneider.

Staff present: James C. Greene, science consultant and Mary Beth McJury, minority counsel.

Mr. **Scheuer**. We have four witnesses and we would like you all to come up and join us at the witness table. We will invite each of you to give your testimony and then after the four of you have testified I am sure we will have some questions for you and you may have some questions for each other.

Dr. Richard A. Griesemer, director of biology, Oak Ridge National Laboratory; Dr. Roger O. McClellan, president of the Lovelace Inhalation Toxicology Research Institute; Dr. Richard B. Setlow, senior biophysicist, Brookhaven National Laboratory; and Dr. Harvey R. Herschman, director, Basic Research and Comprehensive Cancer Center, University of California at Los Angeles.

Dr. **Herschman**. In the Comprehensive Center.

Mr. **Scheuer**. All right. Director of basic research in the Comprehensive Cancer Center, University of California at Los Angeles.

I have a statement that I am going to put in the record. I ask unanimous consent. No objection—so ordered.

[The opening statement of Mr. Scheuer follows:]

OPENING STATEMENT OF
JAMES H. SCHEUER
MARCH 3, 1983

THE SUBCOMMITTEE ON NATURAL RESOURCES, AGRICULTURE RESEARCH AND ENVIRONMENT WILL COME TO ORDER.

ONE OF THE MAJOR HEALTH PROBLEMS FACING AMERICA IS CANCER.

THE DEPARTMENT OF ENERGY HAS A MAJOR RESEARCH EFFORT UNDERWAY TO DETERMINE WHETHER EXPOSURE OF HUMANS TO RADIATION AND CHEMICALS ASSOCIATED WITH ENERGY PRODUCTION AND USE RESULTS IN CANCER.

SINCE CANCER DOES NOT MANIFEST ITSELF UNTIL YEARS AFTER EXPOSURE, LONG-TERM STUDY IS NEEDED.

IN ORDER TO CONDUCT THE NECESSARY RESEARCH, A COMMITMENT TO LONG-TERM FUNDING BY THE

ADMINISTRATION IS ALSO MANDATORY.

IN THE PAST THE ADMINISTRATION HAS MADE THE COMMITMENT WHICH HAS LEAD TO THE EXCELLENT CANCER RESEARCH PROGRAMS WITHIN THE DEPARTMENT OF ENERGY.

HOWEVER, DESPITE THE IMPORTANCE OF UNDERSTANDING THE CAUSES OF CANCER WHICH CAN LEAD TO CURES, FUNDING FOR THIS RESEARCH HAS DECLINED OVER THE PAST TWO FISCAL YEARS.

THE ADMINISTRATION'S FY 1984 BUDGET REQUEST FOR THE DOE ENVIRONMENTAL PROGRAMS IS $210 MILLION WHICH IS TWENTY-ONE PERCENT BELOW THE FY 1982 APPROPRIATION LEVEL OF $267 MILLION.

TODAY'S WITNESSES WILL EXPLAIN SPECIFICALLY HOW THIS BUDGET DECREASE IMPACTS ON THE CANCER RESEARCH PROGRAM.

WHILE I APPLAUD EFFORTS TO REDUCE UNNECESSARY AND DUPLICATIVE EFFORTS, MANY OF THE PROPOSED BUDGET CUTS APPEAR TO BE ARBITRARY, EXCESSIVE, AND WITHOUT MERIT.

FOR EXAMPLE, THE UNITED STATES CONTINUES TO INCREASE ITS USE OF THE VARIOUS TYPES OF ENERGY INCLUDING FOSSIL FUELS, BUT RESEARCH ON CANCER AND THE ENVIRONMENTAL IMPACTS CAUSED BY THE POLLUTANTS HAS DECREASED.

THE AMERICAN PEOPLE DESERVE TO KNOW WHAT THESE CHEMICALS WILL DO TO THEIR HEALTH AND TO THE ENVIRONMENT.

Today's hearing should provide the Subcommittee with an overview of the DOE's cancer related research program, and the impact of the Administration's proposed FY 1984 budget request.

Now, I would like to recognize my distinguished colleague from New York, the ranking minority member of this Subcommittee, Mr. McGrath, for any statement he may wish to make.

I would like to welcome our witnesses today.

We will begin with Dr. Richard A. Griesemer, Director of the Biology Department, Oak Ridge National Laboratory.

Mr. SCHEUER. Would you like to make a statement, Congressman McGrath.

Mr. McGRATH. Yes.

Mr. Chairman, I, too, am pleased to welcome our distinguished witnesses here this afternoon. I would like to extend a special welcome to Dr. Setlow of the Brookhaven National Laboratory. Although the lab is not in my congressional district, I am quite pleased as a Long Island representative to have Dr. Setlow here at this hearing. I ask unanimous consent to revise and extend my remarks and insert my statement in the record at this point.

[The opening statement of Mr. McGrath follows:]

OPENING STATEMENT OF THE HON. RAYMOND J. MCGRATH

HEARING BEFORE THE SUBCOMMITTEE ON NATURAL RESOURCES, AGRICULTURE RESEARCH AND ENVIRONMENT

LINK BETWEEN THE ENVIRONMENT AND CANCER: DOE 's RESEARCH EFFORTS

MR. CHAIRMAN, I, TOO, AM PLEASED TO WELCOME OUR DISTINGUISHED WITNESSES HERE TODAY. I WOULD LIKE TO EXTEND A SPECIAL WELCOME TO DR. RICHARD B. SETLOW OF BROOKHAVEN NATIONAL LABORATORY. THOUGH THE LAB IS NOT IN MY CONGRESSIONAL DISTRICT, I AM QUITE PLEASED TO HAVE LONG ISLAND REPRESENTED AT THIS HEARING.

THE PROGRAMS WE ARE GOING TO HEAR ABOUT ARE VERY IMPORTANT TO THIS COUNTRY. IN ORDER TO MOVE TOWARD FREEING OURSELVES FROM DEPENDENCE ON FOREIGN ENERGY SOURCES, WE ARE SPENDING HUGE SUMS OF MONEY TO DEVELOP OUR COAL RESOURCES AND OTHER ENERGY ALTERNATIVES. AT THE SAME TIME, WE MUST STRIVE TO INSURE THAT THIS DEVELOPMENT DOES NOT HAVE ADVERSE IMPACTS ON OUR HEALTH AND ENVIRONMENT.

I LOOK FORWARD TO HEARING OUR WITNESSES' TESTIMONY ABOUT RECENT RESEARCH BREAKTHROUGHS IN CANCER RESEARCH, AND ALSO FUTURE DIRECTIONS IN THIS FIELD.

Mr. SCHEUER. It's a great pleasure to welcome my friend, my colleague and a distinguished scientist, Dr. Richard B. Setlow.

STATEMENT OF RICHARD B. SETLOW, SENIOR BIOPHYSICIST, BROOKHAVEN NATIONAL LABORATORY

Dr. SETLOW. Thank you, Mr. Chairman. It's a pleasure to be here, gentlemen.

I am a senior biophysicist and Chairman of the Biology Department at the Brookhaven National Laboratory. My credentials in this field go back since graduation from Swarthmore College. At the present time I am a member of the National Academy of Sciences Board on Radiation Effects Research.

I am going to speak about the roles of the Department of Energy in biological research. My viewpoint is that of a basic research scientist and most of the examples I cite come from my experience at Brookhaven. I consider the role of the Department of Energy in biological research to be: one, address long-range problems of concern to DOE, problems such as estimation of the effects of exposures to low doses and dose rates of radiation and of chemicals on human populations. Two, to maintain, use, and keep at the state of the art unique national facilities and instruments designed as research tools for both university and industry scientists.

A General Accounting Office report of January 2, 1981, entitled "Problems in Assessing the Cancer Risks of Low-Level Ionizing Radiation Exposure," may be paraphrased by me. The estimation of low-dose effects, whether radiation or chemical, cannot be done by measurements on humans or on animals, but must be determined by extrapolation from high-dose data on humans and on animals, using theories that relate structures with functions and how functions change when the structures of important biomolecules are altered.

Our research in the Biology Department is concerned with the relations between structures and functions of systems that range in size from molecular through cells to whole animals and plants. The Department has several unique facilities for structure work: the high flux beam reactor, the national synchrotron light source, the scanning transmission electron microscope. Such specialized biophysical devices could not be warranted for individual teaching institutions or industries, but are well justified as national resources available to outside researchers. Although the Department has only 27 scientific staff, there were 97 outside users of our unique facilities last year and an additional 61 investigators visited to collaborate in other scientific areas. It is important that you recognize, however, that a knowledge of structure without an understanding of function is of limited value. Without parallel research on function, there would be a tendency to lose sight of our ultimate goal.

The effects on humans of low doses of radiation or other energy derived hazards are long-range problems of particular concern to DOE. Herein lies the impass: not only are these questions difficult to resolve but they are long-range ones. It was the interest in radiation effects on biological systems that led DOE contractors to the discovery of mechanisms for repairing damage to DNA, the genetic material of cells. These contractors still remain leaders in this research field, which now encompasses wide areas of chemical carcinogenesis, because a number of chemicals mimic radiation in its effects on DNA.

The problems facing the Office of Health and Environmental Research [OHER] of DOE can only be solved by knowing how biological systems work. In reaching for solutions, OHER sponsored research, beginning in 1947, has had a major impact on our approach to and our understanding of biological systems. The various areas of biology cannot be viewed as separate entities, but are all parts of an interacting whole, that I have indicated in a figure on page 4 of my formal testimony. This is a sphere indicating areas that interact strongly with radiation biology. No one field in its isolation could profitably develop by itself. Without radiation biology as a guiding force, other scientific fields would have developed at very slow rates, if at all. Radiation biology, with its quantitative dosimetry, has led the way in determining the dose response relations that are so essential for setting exposure standards. The methodologies devised for doing this quantitative work have led to studies on mutagenesis, chromosomal aberrations and DNA repair and were instrumental in launching the new field of genetic toxicology that is so important now in evaluating the effects of chemical hazards in the environment.

Damage to DNA, resulting from exposure to physical or chemical agents in the environment, can be mutagenic or carcinogenic. We now know that repair mechanisms are able to ameliorate a large fraction of these deleterious effects and as a result reduce the probability of initiating the carcinogenic process by from 10 to 10,000 fold. In 1964 studies with bacteria that were sensitive to DNA damage resulting from ultraviolet, X-ray or chemicals, showed that the sensitivity arose from defects in the ability of these sensitive cells to repair the damage. Repair systems may be thought of as the equivalent of plastic surgery at the molecular level. A bad place in DNA is removed and filled in with the proper components, so that the genetic code is not altered. People with the genetic disease xeroderma pigmentosum have an extraordinarily high prevalence of sunlight-induced skin cancer. It has been shown that these people are deficient in the ability to repair ultraviolet damage. Since then other repair-deficient genetic diseases have been identified. Rather than discussing them, I have appended two reprints describing these diseases.

The defects in DNA repair in xeroderma pigmentosum are associated with a 10,000-fold increase in skin cancer prevalence, but these defects are only about 80 percent. Hence, it is possible that a change in DNA repair of 10 to 20 percent might have large effects, perhaps 10-fold or more on the suspectibility of apparently normal individuals to environmental carcinogens. It is only recently that there has been a recognition of the extensive variation in DNA repair capacity among the apparently normal population. Will people today who repair their DNA better than average do so a year from now? Will those who are slightly defective today be slightly deficient at some later time? Are such differences predictors of disease? We do not know the answers to these questions but they are vital for quantitative evaluation of hazards and for the clues that they might give to enable us to increase the DNA repair capacity of individuals.

It is important to recognize the damage to DNA affects the ability of a cell to reproduce and to use DNA as a good template to make the proper proteins needed for survival. A detailed understanding of these effects requires an intimate knowledge of the sequence of coding units in DNA and how such coding units control the synthesis of normal and aberrant proteins. The only way to approach this problem is by the investigation of simple biological systems. For example, a bacterial virus, known as T7 has been extensively studied at Brookhaven. It contains 39,936—they have all been counted—subunits of DNA. The complete sequence of these 39,936 subunits has now been determined.

Mr. SCHEUER. What's the word after the number?

Dr. SETLOW. Subunits.

Mr. SCHEUER. Subunits.

Dr. SETLOW. Think of them as words.

Mr. SCHEUER. You really can count them?

Dr. SETLOW. Yes. If you know the sequence you must have counted them all—39,936. This was a tour de force. The longest sequence, I should say, accomplished in the world when it was done.

Mr. SCHEUER. When was this accomplished?

Dr. SETLOW. This was accomplished last year.

Mr. SCHEUER. Remarkable.

Dr. SETLOW. It should be possible now to use this information to discover subtle changes in replication and control of synthesis that may result in slight changes in the genetic code.

It is important that you recognize that other Government agencies draw on the expertise of the biological research groups supported by the Department of Energy. I give three examples from Brookhaven:

One, the Biology and Medical Department in cooperation with the Pathology Department, State University of New York at Stony Brook, have moneys from the National Cancer Institute to train postdoctoral students in the field of environmental and genetic aspects of neoplasis;

Two, the Biology Department has a contract with the National Cancer Institute to investigate low-level radiation effects and low-dose rate effects. This work is being done by counting mutations in a singular plant called tradescantia, the spiderwort, it blooms in everyone's backyard. This plant is sensitive enough to permit quantitative measures down to doses of less than 1 rad of X-rays. It is an ideal test system to check out theories of radiation action. Some people might object that extrapolation from plants from plants to animals is not possible, but one must remember that biology has theories just as physics does and the reactions of the genetic material, DNA, in one organism are very similar to those in another;

Third, the Biology and Medical Department have a contract with the National Cancer Institute to investigate the repair and the cytogenetic responses of human cells derived from cancer-prone families.

The above endeavors complement and enhance those supported by DOE, but they would not be possible without the existence of DOE support.

I hope it is clear from this brief review that biological research supported by DOE is of high caliber and is relevant to a number of national interests.

I believe that DOE through its Office Health and Environmental Research has helped us develop, and to use, unique capabilities for experimental studies which will provide answers to long-range questions of importance to energy technology. The research groups that DOE supports at the national laboratories and at universities are an important national resource.

We have estimates at the present time that our budgets will be cut in the coming fiscal year. Rather than get into the details of such cuts I would simply say that from my point of view, such cuts would devastate a research program that is generally agreed to be excellent, relevant, and appropriate, they spell ERA, for a national laboratory.

[The prepared statement of Dr. Setlow follows:]

ROLES OF THE DEPARTMENT OF ENERGY IN BIOLOGICAL RESEARCH

Richard B. Setlow*

INTRODUCTION

My viewpoint is that of a basic research scientist and most of the examples I cite come from my recent experiences at the Brookhaven National Laboratory. I consider the role of DOE in biological research is to:

1) Address long range problems of concern to DOE, problems such as the estimation of the effects of exposures to low doses and dose rates of radiation and chemicals on human populations

2) Maintain, use, and keep at the state-of-the-art unique National facilities and instruments designed as research tools for both university and industry scientists.

---

*I am a Senior Biophysicist and the Chairman of the Biology Department at the Brookhaven National Laboratory. The Laboratory is operated by Associated Universities, Inc. for the U. S. Department of Energy. I was a member of the faculty of the Physics Department at Yale University from 1943 to 1960. From 1961 to 1974 I was a member of the staff of the Biology Division of the Oak Ridge National Laboratory and of the faculty of the University of Tennessee. I have been at Brookhaven since 1974 and am an Adjunct Professor of Biochemistry at the State University of New York at Stony Brook. My research since 1950 has involved the effects of radiation on molecules, viruses, cells, and animals. I am a member of the National Academy of Sciences Board on Radiation Effects Research. My detail curriculum vitae is appended.

A General Accounting Office report of January 2, 1981 entitled "Problems in Assessing the Cancer Risks of Low-Level Ionizing Radiation Exposure," Vol. 1, pg. IV, said:

> "GAO believes that molecular and cellular studies, supported by selected animal experiments, are likely to provide important insights into the mechanisms by which radiation causes cancer. GAO's work indicates that mechanisms research, particularly on molecular and cellular effects, warrants increased emphasis and priority."

and on pg. V, one of their recommendations was:

> "Ensure, in research on ionizing radiation exposure, that increased priority and emphasis are given to studying the mechanisms of cancer induction through cellular and molecular studies and other fundamental research."

A paraphrase of this two-volume report is that the estimation of low-dose effects, whether radiation or chemical, cannot be done by measurements on humans or on animals, but must be determined by extrapolation from high-dose data on humans and on animals using theories that relate structures with functions and how functions change when the structures of important biomolecules are altered.

STRUCTURE AND FUNCTION

Our research in the Biology Department is concerned with the relations between structures and functions of biological systems that range in size from molecular through cells to whole animals and plants. The Department has several unique facilities for this work--the High Flux Beam Reactor, the National Synchrotron Light Source, and the Scanning Transmission Electron Microscope. Such specialized biophysical devices could not be warranted for individual teaching institutions or industries, but they are well justified as National resources available to outside researchers. Although the Department has only 27 scientific staff, there were 97 outside users of our unique facilities last year and an additional 61 investigators visited to collaborate in other scientific areas. The unique facilities will form the core of a Center for Structural Biology at Brookhaven and will provide us with information on all types of biological structures. But a knowledge of structure without an understanding of function is of limited value because without parallel research on function, there would be a tendency to lose sight of our ultimate goal. As a matter of practicality, our innovative staff would leave if they were not surrounded by other good scientific investigators.

RADIATION BIOLOGY

The effects on humans of low doses of radiation or other energy derived hazards are long range problems of particular concern to DOE. Herein lies the impasse: not only are these questions difficult to resolve but they are long-range ones. In many instances the experiments are not amenable to student dissertations because of the long times involved in the work. It was the interest in radiation effects on biological systems that led DOE contractors to the discovery of mechanisms for repairing damage to DNA, the genetic material of cells. These contractors still remain leaders in this research field, which now also encompasses wide areas of chemical carcinogenesis, because a number of chemicals mimic radiation in its effects on DNA.

The problems facing the Office of Health and Environmental Research (OHER) of DOE are general biological ones. They can only be solved by knowing how biological systems work. In reaching for solutions, OHER sponsored research, beginning in 1947, has had a major impact on our approach to and our understanding of biological systems. The various areas of biology cannot be viewed as separate entities, but are all part of an interacting whole indicated in Figure 1. Without Radiation Biology as a guiding force, other scientific fields would have developed at very slow rates, if at all.

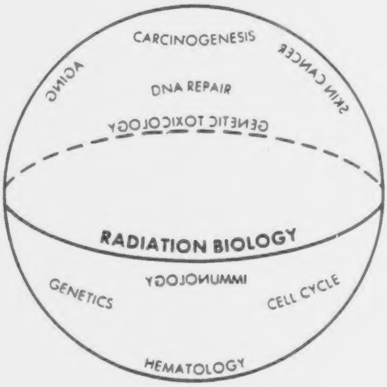
CARCINOGENESIS
AGING
SKIN CANCER
DNA REPAIR
GENETIC TOXICOLOGY
RADIATION BIOLOGY
IMMUNOLOGY
GENETICS
CELL CYCLE
HEMATOLOGY

Fig. 1 Some research areas that interact strongly with Radiation Biology. The spherical surface is designed to show that there are strong interactions among many fields of biology and that no one field in isolation could profitably develop by itself.

Radiation Biology, with its quantitative dosimetry, has led the way in determining the dose response relations that are so essential for setting exposure standards. The methodologies devised for doing quantitative work on mutagenesis, chromosomal aberrations and DNA repair were instrumental in launching the new field of genetic toxicology that is so important now in evaluating the effects of chemical hazards in the environment.

DNA DAMAGE AND ITS REPAIR

Damage to DNA, the genetic material of cells, resulting from exposure to physical or chemical agents in the environment, can be mutagenic and carcinogenic. We now know that repair mechanisms are able to ameliorate a large fraction of these deleterious effects and, as a result, reduce the probability of initiating the carcinogenic process in humans by from 10 to 10,000-fold. Let me elaborate on this latter point, drawing heavily on my own research experience. In 1964 studies with bacteria that were very sensitive to DNA damage resulting from ultraviolet, x-rays, or chemicals, showed that the sensitivity arose from defects in the ability of these sensitive cells to repair the damage. Repair systems, and there are a number of them, may be thought of as the equivalent of plastic surgery at the molecular level. A bad place is removed and filled in with the proper components, so that the genetic code is not altered. People with the genetic disease xeroderma pigmentosum have an extraordinarily high prevalence of sunlight-induced skin cancer. In 1968 it was shown that these people were deficient in the ability to repair ultraviolet damage. Since then other repair-deficient genetic diseases have been identified as shown by increased sensitivity to x-rays, and sensitivity to chemical carcinogenic agents. I have appended two reprints of mine giving more details about some of these diseases. One is on "Repair Deficient Human Disorders and Cancer," the second is on "DNA Repair, Aging, and Cancer."

The defects in DNA repair in xeroderma pigmentosum that are associated with a 10,000-fold increase in skin cancer prevalence are about 80%. Hence, it is possible that a change in DNA repair of 10-20% might have large effects, perhaps 10-fold or more, on the suspectibility of apparently normal individuals to environmental carcinogens. It is only recently that there has been a recognition of the extensive variation in DNA repair capacity among the apparently normal population. Will people who today repair their DNA better than average do so a year from now? Will those who are slightly defective in DNA repair today be slightly deficient at some later time? Are such differences predictors of disease? We do not know the answers to these questions but they are vital for quantitative evaluation of hazards and for the clues that they might give to enable us to increase the DNA repair capacity of individuals.

Sensitivities to chemical agents often mimic radiation sensitivities. It has recently been found that the repair of a particular kind of chemical damage—the addition of a methyl group to an oxygen atom of the DNA component guanine—takes place by the rapid transfer of the methyl group to a repair protein in the cell. In the process the repair protein is used up and it is no longer available for further reactions. Thus at low doses, repair is very effective, but at high doses the system becomes saturated. One expects, therefore, that for such reactions there will appear to be a threshold dose below which there is a very small effect and above which the effect increases very rapidly with dose.

THE SEQUENCE OF DNA

Damage to DNA affects the ability of the cell to reproduce and to use DNA as a good template to make the proper proteins needed for survival. A detailed understanding of these effects requires an intimate knowledge of the sequence of coding units in DNA and how such coding units control the synthesis of normal or aberrant proteins. The only way to approach this problem is by investigation of simple biological structures. For example, a bacterial virus, known as T7 has been extensively studied at Brookhaven for its genetics and its effects on cells. It contains 39,936 subunits—base pairs—of DNA. The complete sequence of these 39,936 units has now been determined and it should be possible to use this information to discover subtle changes in replication and control of synthesis that may result in slight changes in the genetic code.

COOPERATION WITH OTHER GOVERNMENT AGENCIES

Other Government agencies draw on the expertise of the biological research groups supported by DOE. I give four examples from Brookhaven:

1) The Biology and Medical Departments in cooperation with the Pathology Department, State University of New York at Stony Brook have monies from the National Cancer Institute to train postdoctoral students in the field of environmental and genetic aspects of neoplasia;

2) The Biology Department has a contract with the National Cancer Institute to investigate low-level radiation effects and low dose rate effects. This work is being done by counting mutations in a singular plant called Tradescantia, the spiderwort, which is sensitive enough to permit quantitative measurements down to doses of less than 1 rad of x-rays. It is an ideal test system to check out theories of radiation action. Some people might object that extrapolation from plants to animals is not possible, but one must remember that biology has theories just as physics does and the reactions of the genetic material, DNA, in one organism are very similar to those in another;

3) The Biology and Medical Departments have a contract with NCI to investigate the repair and the cytogenetic responses of human cells derived from cancer-prone families. It is of interest that NCI supports similar but not identical repair studies at a Canadian National Laboratory--Chalk River;

4) Problems involving recombinant DNA technology were of great concern to society several years ago. Jane Setlow of the Biology Department, was a member of the NIH Recombinant DNA Advisory Committee from 1974 to 1981 and was its Chairman in 1980 and 1981.

The above endeavors complement and enhance those supported by DOE, but they would not be possible without the existence of DOE support.

CONCLUSIONS

I hope it is clear from this brief review that biological research supported by DOE is of high caliber and is relevant to a number of national interests.

I believe that DOE through its Office of Health and Environmental Research has helped us to develop, and to use, unique capabilities for experimental studies which will provide answers to long range questions of importance to energy technology. The research groups that it supports at the National laboratories and at universities are an important National resource.

The future benefits to be gained by OHER support in Radiation Biology include: 1) a detailed understanding of the relations between structure and function resulting from the use of powerful National facilities devoted to such problems; 2) a new set of exposure standards for neutron irradiation (it seems that the present atomic bomb data are inadequate for this purpose); 3) an estimate of induced mutation rates in humans exposed to both chronic and acute doses based on basic biological knowledge and theories of radiation and chemical action; and 4) measurements of the variations in the ability of humans to repair damages to their DNA, so providing estimates not only of the average response in the population but of sensitive subsets in the population. Undoubtedly the outcome of even this limited number of specific goals is bound to be much greater than answers to the questions asked.

DOE's present budget estimate for FY 1984 for Brookhaven's research program in biological structures and in cancer research is 11% below FY 1983. The budget for FY 1983 is at present 4% below that for FY 1982. From my point of view, such cuts would devastate a research program that is generally agreed to be excellent, relevant and appropriate for a National laboratory.

CURRICULUM VITAE

Richard B. Setlow

Born January 19, 1921, New York, New York

1941	A.B., Swarthmore College	Physics
1947	Ph.D., Yale University	Physics
1943-1947	Yale University Physics Department	Instructor
1947-1956	Yale University Physics Department	Assistant Professor
1954-1959	Yale University	Director of Undergraduate Studies in Physics and in Biophysics
1956-1961	Yale University Physics and Biophysics Departments	Associate Professor
1961-1974	Oak Ridge National Laboratory Biology Division	Biophysicist
1964-1969	Oak Ridge National Laboratory Biology Division	Group Leader, Biophysics
1969-1974	Oak Ridge National Laboratory Biology Division	Scientific Director Biophysics and Cell Physiology
1967-1974	University of Tennessee	Professor of Biomedical Sciences
1972-1974	University of Tennessee	Director, Univ. of Tenn. Oak Ridge Graduate School of Biomedical Sciences
1974-	Brookhaven National Laboratory Biology Department	Senior Biophysicist
1975-	State University of New York at Stony Brook	Adjunct Professor of Biochemistry
1979-	Brookhaven National Laboratory Biology Department	Chairman Biology Department

Richard B. Setlow

Memberships: National Academy of Sciences
Biophysical Society
Radiation Research Society
American Society for Photobiology
American Society of Biological Chemists
Environmental Mutagen Society
AAAS
Phi Beta Kappa
American Academy of Arts and Sciences
American Association for Cancer Research

Other Activities:

President: Biophysical Society, 1969-1970
V International Congress on Photobiology, 1968
Comite International de Photobiologie, 1972-1976

Vice-President: Comite International de Photobiologie, 1968-1972

Member of Commission on Radiation Biophysics of IUPAB, 1969-1975
Commission on Radiation and Environmental Biophysics of IUPAB, 1970-1974

Councillor in Physics of International Association of Radiation Research, 1970-1974

NAS-NRC Committee: Photobiology, Chairman, 1965-1970
Phototherapy in the Newborn, 1972-1975
Climatic Impact of SST, 1972-1975
Panel to Review Statistics on Skin Cancer, 1974-
Space Science Board, 1975-1978
Solar Power Satellite Systems, 1979-1981
Federal Research on Biological and Health Effects of Ionizing Radiation, 1980-1982
Biological Effects of Increased Solar Ultraviolet Radiation, Chairman, 1981-1982
Board of Research on Effects of Radiation, 1981-

Past Council Member: Biophysical Society
Radiation Research Society

Editorial Boards: Photochemistry and Photobiology (past)
Radiation Research (past)
Biophysical Journal (past)
Cancer Research (past)
BioScience (past)
Mechanisms of Ageing and Development (present)
Mutation Research (DNA Repair Reports) 1983-1985

Member of Advisory Committees: Division of Biological and Medical Research,
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Biology Department
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Carcinogenesis (Franklin Institute), 1978-

Member: NIEHS Program Planning Group B - Injury Patterns and Mechanisms, 1978-1979

Awards: Radiation Research Society Eleventh Failla Memorial Lecture, "The Repair of DNA — Its Past and Its Future" at 21st Annual Meeting, St. Louis, Missouri, April 29 - May 3, 1973.

Finsen Medal for outstanding fundamental contribution to Photobiology and Repair of Nucleic Acids, at 8th International Congress on Photobiology, Strasbourg, France, July 20-25, 1980.

Richard B. Setlow

Selected Publications

Margenau, H. and ________. 1945. Atomic and molecular theory since Bohr: Resume of specific results. Amer. J. Phys. 13, 73-95.

________. 1955. Radiation studies of proteins and enzymes. Ann. N. Y. Acad. Sci. 59, 471-483.

________ and Pollard, E. 1962. "Molecular Biophysics", Addison Wesley Publishing Co., 545 pages.

________ and Carrier, W. L. 1964. The disappearance of thymine dimers from DNA: A error-correcting mechanism. Proc. Natl. Acad. Sci. 51, 226-231.

________, Regan, J. D., German, J., and Carrier, W. L. 1969. Evidence that Xeroderma pigmentosum cells do not perform the first step in the repair of ultraviolet damage to their DNA. Proc. Natl. Acad. Sci. 64, 1035-1041.

________ and Carrier, W. L. 1973. Endonuclease activity toward DNA irradiated in vitro by gamma rays. Nature New Biology 241, 170-172.

________. 1974. The wavelengths in sunlight effective in producing skin cancer: A theoretical analysis. Proc. Natl. Acad. Sci. 71, 3363-3366.

Hart, R. W., ________, and Woodhead, A. D. 1977. Evidence that pyrimidine dimers in DNA can give rise to tumors. Proc. Natl. Acad. Sci. USA 74, 5574-5578.

________. 1978. Repair deficient human disorders and cancer. Nature 271, 713-717.

________. 1982. DNA repair, aging, and cancer. Natl. Cancer Inst. Monogr. 60, 249-255.

Waldstein, E. A., Cao, E.-H., and ________. 1982. Adaptive resynthesis of O^6-methylguanine-accepting protein can explain the differences between mammalian cells proficient and deficient in methyl excision repair. Proc. Natl. Acad. Sci. USA 79, 5117-5121.

Waldstein, E. A., Cao, E.-H., Miller, M. E., Cronkite, E. P., and ________. 1982. Extracts of chronic lymphocytic leukemia lymphocytes have a high level of DNA repair activity for O^6-methylguanine. Proc. Natl. Acad. Sci. USA 79, 4786-4790.

DNA Repair, Aging, and Cancer[1, 2]

Richard B. Setlow[3]

ABSTRACT—The ability of cells to repair UV damage to DNA is closely associated with a reduction in skin cancer incidence, and the quantitative epidemiological data indicate that proficient repair systems reduce cancer incidence by as much as 10,000-fold. The latter decrease corresponds to an equivalent reduction in UV dose of sevenfold to twentyfold. Older cells may accumulate DNA damage, but this accumulation does not seem to be the result of a deterioration of the repair systems studied to date. Although a correlation has been described between life-span and the proficiency of nucleotide excision repair and the association between cellular aging and decreasing repair is much weaker, no definitive data indicate whether these relations are causal ones.—Natl Cancer Inst Monogr 60: 249–255, 1982.

The integrity of DNA or certain of its sequences is important for the fidelity of transcription and replication and all the biological processes that depend on reading the DNA code. Hence agents that react with DNA are potentially dangerous. An important problem for us is how to assess the magnitude of such dangers. As a start to such an analysis, we need to know how particular DNA adducts affect mutation, cancer, and aging. The answers to these questions have eluded us even for extensively studied damaging agents such as ionizing radiation. Thus as a beginning, we desire to know the shape of the dose–response curve (dose measured in DNA adducts) and how such a curve depends on age, other factors in the environment, and tumor promoters (text-fig. 1).

To make a choice among potential dose–response curves is impossible unless we have a basic understanding of the molecular and cellular mechanisms relating changes in DNA to biological responses. Moreover, as indicated in text-figure 1, it is important for one to have some estimate of the background level of the biological effect so as to estimate the relevant importance of DNA adducts in changing such an effect. One reason for emphasizing DNA damage is that the genetic diseases XP, ataxia-telangiectasia, Fanconi's anemia, and Bloom's syndrome are associated with an increase in cancer risks and with defects in DNA metabolism or repair [(*1, 2*); table 1]. The best understood of these diseases is XP, although we are still ignorant of the molecular details involved in the defect. Moreover, the etiologic agent is known to be sunlight, and all the available evidence indicates that it is the short wavelength UV in sunlight that is the damaging agent. As we shall see below, we can obtain dose–response relationships for the average population and estimate the effect of DNA repair in reducing the level of DNA damage. The UV damage is emphasized not only because of its relatively good dosimetry but also because of the wealth of information from prokaryotic systems on the effects of UV damage and the repair of that damage. Moreover, UV seems to be a good model for the many chemicals that give rise to bulky DNA adducts, such as those of fluorenylacetamide and benzo[*a*]pyrene (*1, 4*); such adducts mimic UV in a number of ways (*see* table 2).

It would be most useful if other repair-deficient diseases would provide models for other types of DNA damage, although it is worth noting that ataxia-telangiectasia cells, which are sensitive to ionizing radiation, are hypomutable to X-rays (*6*).

TYPES OF DNA REPAIR

Because replication or transcription on a damaged template is bad, one can eliminate the subsequent problems by stopping all replication and transcription. However, this is self-defeating for living systems. Hence mechanisms for repairing parental DNA or the DNA replicated on a damaged template are important. The latter type of repair, called "postreplication repair," plays a role in mutagenesis in prokaryotic systems, but its role and the molecular mechanisms involved are poorly understood in the eukaryotic ones. Mechanisms for repair of parental DNA are shown in text-figures 2 and 3 (*1*). Text-figure 2 shows base excision repair, a process in which the essential attack is not on the polynucleotide chain. Text-figure 3 shows nucleotide excision repair in which the initial attack seems to be on the polynucleotide chain, although recent evidence indicates that in some purified enzyme systems a glycosylase may act on a pyrimidine dimer before the endonuclease attack (*8, 9*). A common method of estimating the magnitude of DNA repair is by the incorporation of [^{3}H]dThd during repair synthesis as indicated by the solid black lines in text-figures 2 and 3. Obviously, two of the pathways of base excision repair (a and b) cannot be assessed by this means.

The details of the several steps in excision repair are not well understood for eukaryotic systems. In prokaryotes, a methyl-accepting protein has been identified that works to remove O^6-methylguanine stoichiometrically, whereas the other activities seem to be enzymatic in nature (*10*).

ABBREVIATIONS: XP = xeroderma pigmentosum; UDS = unscheduled DNA synthesis; J = joule(s).

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[2] Supported by contract DE-AC02-76CH00016 with the United States Department of Energy.

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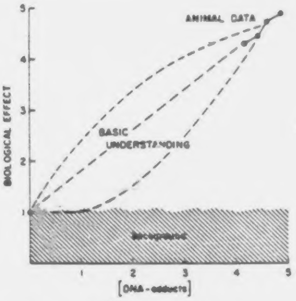
TABLE 1.—*Repair deficient diseases*[a]

Disease	Frequency		Cancer probability[b]		Etiologic agent	Cell sensitivity	Repair deficiencies
	Homozygote	Heterozygote	Homozygote <20 yr old	Heterozygote			
XP	1/300,000	1/300	Skin cancer = >0.5 (melanoma = >0.1)	Fivefold normal in the South	Sunlight	UV and mimetics	One or more of excision, photoreactivation, and postreplication (≥ 7 groups)
Ataxia-telangiectasia	1/40,000	1/100	0.1 (lymphoreticular = 0.06; leukemia = 0.02)	Fivefold normal <45 yr; 50% greater mortality than average	?	X-rays, alkylating agents	Some cell strains defective in "X-ray" repair (≥ 3 groups)
Fanconi's anemia	1/300,000	1/300	Tenfold normal	Like normal	?	Cross-linking agents	Some cell strains defective in cross-link repair

[a] *See* (*3*).

[b] Approximate average cancer probabilities: Skin cancer prevalence = 0.005; melanoma incidence = 6×10^{-5}/yr; lymphoreticular cancer = 13×10^{-5}/yr; leukemia (t_{max} ~4 yr) = 42×10^{-6}/yr.

In human cells, the excision of UV-induced pyrimidine dimers is a complicated function of dose and time as indicated in text-figure 4 (*11*). Normal cells are much more proficient in the process than are XP cells, and, for both types of cells, the rate of excision becomes saturated at high doses. The strange kinetics for normal cells in text-figure 4A are presumably related to the more rapid excision of dimers from the linker region of chromatin. The rates shown are the maximum possible. A larger dose will not result in an increase in the number of dimers removed because the rate of repair saturates as expected for an enzymatic reaction. The percentage of dimers removed in a given time decreases with increasing dose as indicated in text-figure 4B. Although most normal fibroblast strains appear similar in their excision ability, variations in repair, estimated by UDS, have been reported in leukocyte cultures (*12*). The variation among the human population is not well-known. One can use the data in text-figure 4 to estimate the average maximum number of pyrimidine dimers that can be removed per hour. For normal cells this is about 8×10^4/hour/cell and for XP C-cells it is about 10^4/hour/cell. One can estimate from the intensity of noon sun in Texas in September (*13*) that such light would make approximately 5×10^4 dimers/hour/skin cell. These numbers indicate that excision repair in normal fibroblasts is able to keep up with the steady state of production of dimers, whereas XP C-cells fall far behind.



TEXT-FIGURE 1.—Hypothetical relations between the concentration of DNA adducts in cells and biological effects. Three possible dose-response curves are shown joining the background value observed at zero adducts and animal data obtained at high adduct concentrations.

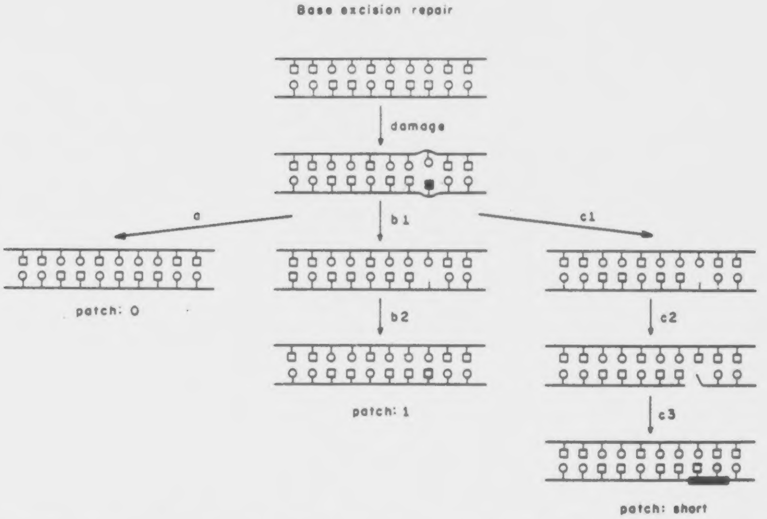
SKIN CANCER

Many factors, such as age, genetic background, occupation, and the exposure to the UV in sunlight, are involved in the incidence of nonmelanoma skin cancer. The UV exposure itself is complicated because it changes with the time of day, time of year, and latitude. An added complication is

TABLE 2.—*Ways in which some chemical damages mimic UV damage in human cells*[a]

1) Cells sensitive to UV (XP) are more sensitive to the chemical than are normal cells.
2) Chemically treated viruses show a higher survival on normal than on XP cells.
3) The XP cells deficient in repair of UV damage are also deficient in excision of chemical damage.
4) Excision repair of UV and of chemical damage involves long patches (~100 nucleotides).
5) The XP complementation groups observed for repair of chemical damage are the same as those for UV damage.

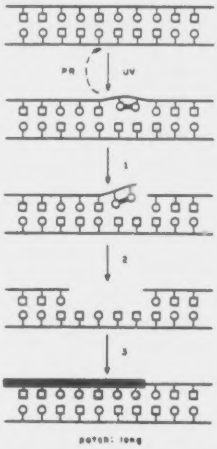
[a] *See* (*5*).



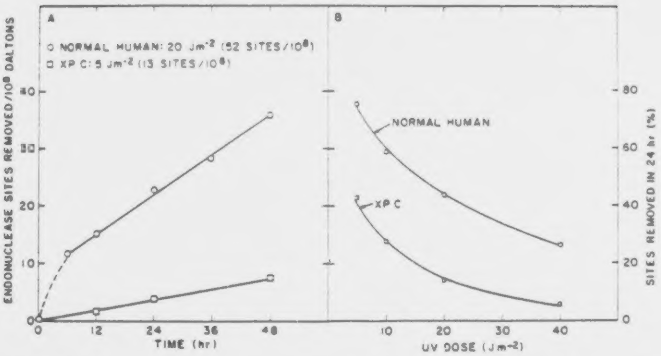
TEXT-FIGURE 2.—A schematic picture illustrating various possibilities for base excision repair. *Circles* represent pyrimidines and the *squares* purines. *Solid square* is an altered purine (perhaps an alkylated one). *Solid line* in *pathway c* represents repair replication or UDS (*7*).

the necessity of knowing the effective wavelengths in sunlight and what the effective UV dose would be. The sensitivity for cancer production as a function of wavelength is not known, but if we assume that the sensitivity parallels that for affecting DNA (*14*), then we can use one of the many action spectra for cell killing as representative, on a theoretical basis, of what the action spectrum for cancer initiation should be. One may then use such data to calculate the average annual UV fluence at different locations in the United States and correlate such fluences with epidemiological data obtained at similar locations. The best correlation is made if one takes nonmelanoma skin cancer incidence to be an exponential function of dose (*15*). Typical recent data are shown in text-figure 5 [*see* (*16*)]. The exponential nature of these dose-response data are shown for the age-adjusted population, but similar correlations hold for age-specific rates (*15*). The comparison of recent with previous data indicates that skin cancer incidence is increasing with time, perhaps because of changing life styles. The average dose in text-figure 5 is given in terms of a measure of erythemal effectiveness. Such a scale gives more weight to the longer wavelengths than would a DNA-weighted dose. The erythemal dose changes by a factor of 2 from one end of the United States to the other. The annual DNA dose changes by 2.5 to 3.

One can make an estimate of the effects of DNA repair, i.e., photoreactivation, excision, and postreplication repair, in ameliorating the effects of UV radiation in the production

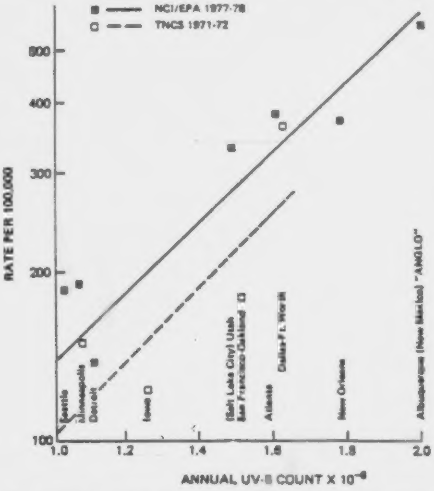


TEXT-FIGURE 3.—A schematic diagram of nucleotide excision repair of pyrimidine dimers resulting from UV irradiation. PR represents the enzymatic monomerization of such dimers and requires the presence of light (*7*).



TEXT-FIGURE 4.—The removal of endonuclease sensitive sites (a sensitive measure of the number of pyrimidine dimers in DNA) from the DNA of normal human and XP C-cells, as a function of time for a given dose (A) or as a function of dose at a given time (B). Text-figure is reproduced with permission of the publisher (*11*).

of skin cancer by the procedure diagrammed in text-figure 6. Inasmuch as incidence and prevalence of skin cancer increase exponentially with dose, we can extrapolate from age-specific data (*17*) to estimate the prevalence in the average white population younger than 20 years old and, through this point on the graph, extrapolate over a range of 10^4 so as to determine the fluence that gives a prevalence equivalent to that observed in XP, i.e., 0.5 (data are not shown). This fluence, which is approximately 2.15 on the scale shown in text-figure 6, is sevenfold greater than the average fluence to which the population is exposed. If one makes the reasonable assumption that individuals with XP receive less exposure, e.g., one-third of the average noted in the United States, because of their extreme sensitivity to sunlight, we conclude that the dose to the average population necessary to give the same prevalence as in XP is about twentyfold greater than that to which patients with XP are exposed. Hence DNA repair modifies the effective dose by between sevenfold and twentyfold, and this modification changes the prevalence of nonmelanoma skin cancer by a factor of approximately 10^4.



TEXT-FIGURE 5.—The age-adjusted incidence of nonmelanoma skin cancer in the United States as a function of annual UV dose weighted according to an approximate erythemal action spectrum. These are preliminary data from Scotto and Fears given in (*16*). NCI/EPA = National Cancer Institute/Environmental Protection Agency; TNCS = Third National Cancer Survey.

AGING

Ever since the work of Price et al. (*18*) showing, by an indirect enzymatic test, that DNA single-strand breaks measured under denaturing conditions appear in cells of aging animals, investigators have attempted to link causally DNA damage and aging and to find a relationship between DNA repair capability and the control of the rate of accumulation of damage. Table 3 shows estimates of the number of changes introduced into mammalian cells per hour at 37° C from data extrapolated from the effects on DNA in vitro (*19, 20*). Whether the accumulation of this much damage is bad or not depends on the rates of repair. In normal human cells, the rates that have been measured are appreciably greater than those shown in table 3. Normal cells can repair 8×10^4 dimers/hour and most of the single-strand breaks in DNA that result from 10,000 rad in 60 minutes (*21*).

Three types of experiments, performed in our attempts to relate repair and aging, include measurements on cells 1) of

TABLE 3.—*Estimated numbers[a] of changes introduced into mammalian cell DNA[b] per hr*

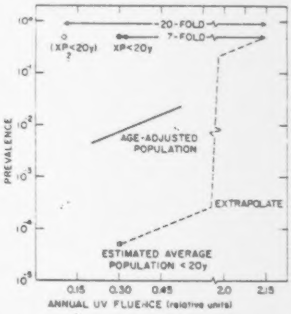
Types	No. of changes
Deamination	30
Depyrimidination	100
Depurination	2×10^3
Single-strand nicks (in alkali)	8×10^3

[a] Estimates were made at pH 7.4 and 37° C. Data are from T. Lindahl (*19*) and R. Shapiro (*20*).

[b] Values are for 6×10^{12} daltons/cell.

different ages in culture; 2) from old and young animals of the same species; and 3) of the same relative age from different species. Unfortunately, a large number of measurements have used UV as the model damage and not the predominant ones, indicated in table 3, that accumulate by heat stress. Researchers use UV because it is easy to introduce into cells, and the numbers of damages are easy to measure. However, its repair is by a long patch mechanism and not by one of the short patch types associated with the repair of apurinic sites (*4*) illustrated in text-figures 2 and 3.

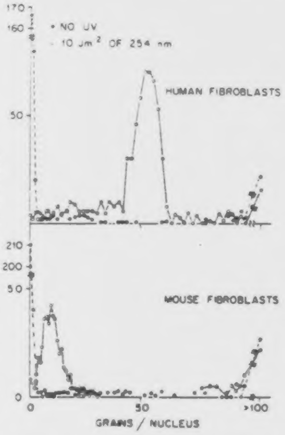
Most UV experiments have used UDS as the measure of repair. Irradiated cells in the non-S-phase of the cell cycle or cells whose normal DNA synthesis is inhibited by hydroxyurea are exposed to [^{3}H]dThd, and the incorporation of label is determined either with the use of a scintillation counter or by radioautography. The latter method is the better one because one can distinguish easily between a normal and an abnormal distribution of repair synthesis among cells. Typical data by which human and mouse fibroblasts are compared are shown in text-figure 7 (*22*). In the absence of UV irradiation, almost all cells show 0 grains/nucleus. After UV irradiation, almost all cells show appreciable UDS, and it is apparent that human fibroblasts show much more UDS than do mouse fibroblasts. This result is not a peculiarity of UDS measurements because determinations of the loss of endonuclease-sensitive sites (pyrimidine dimers) from the skin of irradiated humans indicates a rapid repair (*23*), whereas the loss from irradiated mouse skin is minute (*24*).



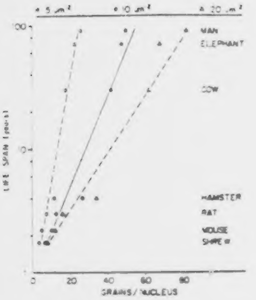
TEXT-FIGURE 6.—A schematic way for determination of the effects of DNA repair by dose modification factor or of the ratio of the doses to the average population and to patients with XP to yield the same prevalence as that of nonmelanoma cancer. Annual UV fluence is that appropriate for an effect on DNA. It is assumed that the dose-response curve is exponential, as is indicated for the age-adjusted population.

Experiments such as those shown in text-figure 7 have been done with cells from a number of species. Data from one such set of experiments (*22*) are shown in text-figure 8. They indicate that the amount of repair, estimated by UDS, is directly associated with life-span. Long-lived animals are better at repair of UV damage than are short-lived ones. Several other experiments (*25–28*) confirm the association shown in text-figure 8, although some differences are observed in quantitative results. One experiment on a large number of mammalian species did not find such an association (*29*). Thus although the magnitude of the association between the ability to repair UV damage and life-span is not clear, the existence of an association among mammalian species is.

However, several arguments indicate that the association shown in text-figure 8 is not a causal one. For example, XP cells have the same life-span in culture as do normal cells (*30*), and individuals with XP do not age prematurely, although their sun-exposed skin does. Moreover, fibroblasts from older people show no large change in UDS capacity (*30*), although the correlation is weak between a decrease in UDS in lymphocytes after UV irradiation and the age of the individual (*31*). Perhaps the best argument against a causal relationship between DNA excision repair and life-span comes from investigations of species other than mammals



TEXT-FIGURE 7.—Distribution of grains among human and mouse fibroblasts unexposed and exposed to UV and subsequently incubated in [^{3}H]dThd and hydroxyurea for 8 hr. This is a typical type of UDS measurement (*22*).



TEXT-FIGURE 8.—UDS in young fibroblasts exposed to 254 nm. The association between UDS resulting from UV irradiation, indicated by grains/nucleus, and life-span of a number of mammalian species (*22*). The association holds for all the UV doses tested.

(*32*); table 4 shows such data. The comparison of fish and turtles with mammals indicates that no association between repair and life-span exists. Therefore, we concluded that nucleotide excision does not determine life-span. Perhaps short-lived mammals do not need such a system and turn it off early in their development (*33*). In any event, the stress imposed on animals by UV is negligible, and the ambient concentration of UV mimetics is trivial. It would be surprising indeed if excision repair were related to life-span; if it were, the construction by genetic engineering techniques of a mouse proficient in nucleotide excision repair would be of great gerontological interest.

Late passage human cells show appreciably less UDS than do those in early passage after treatment with UV, gamma-rays, or in *N*-acetoxy-2-fluorenylacetamide (*34*). The late passage populations are heterogeneous, with some cells doing appreciable UDS and others close to zero. However, measurements on the same cells of scheduled DNA synthesis with the use of a double-label technique indicate that cells deficient in UDS are also deficient in scheduled synthesis (*34*). Both decrease together. The reasons for the decrease are not known, but one might be the inability to form nucleoside triphosphates. Thus in this type of experimental system, no causal relationship is indicated between nucleotide excision repair and aging. It looks more as if repair decreases because cells age.

TABLE 4.—*Excision repair of UV damage by cells in culture*[a]

Cells	Life-span of species, yr	Dimers excised in 24 hr, %
Normal human	100	60
Mouse	2-3	5
Amazon molly	3	~5
Rainbow trout	8	~0
Box turtle	~100	~5

[a] Cells were exposed to 10-20 Jm^{-2} of 254 nm (*11, 22, 32*).

Further experimental work on possible relations between DNA repair and aging should involve investigations of the role of base excision repair because, as indicated in table 3, such types of damage are more likely to occur during normal metabolism.

CONCLUSIONS

A review of the findings produced the following:

1) Damage to DNA is bad and can result in initiating events in cancer.

2) DNA repair mechanisms can reduce the effective UV dose to humans by approximately tenfold or more and, as a result, decrease the cancer incidence by 10^4-fold. These large effects probably arise because most of us are normally exposed to UV doses that induce much damage to DNA, a situation which is much different from those incurred from ambient chemicals.

3) Older cells accumulate damage, but the ability to repair DNA by nucleotide excision is *not* a causal event in in vitro or in vivo aging.

4) UV damage and its repair have been extensively studied and are fairly well understood, but it is probably *not* the proper model, if indeed there is one, for DNA damage and aging except for the skin of those extensively exposed to sunlight.

REFERENCES

(*1*) SETLOW RB: Repair-deficient human disorders and cancer. Nature 271:713-717, 1978

(*2*) FRIEDBERG EC, EHMANN UK, WILLIAMS JI: Human diseases associated with defective DNA repair. Adv Radiat Biol 8:85-174, 1979

(*3*) SETLOW RB: Different basic mechanisms in DNA repair. Arch Toxicol 3 (Suppl):217-228, 1980

(*4*) REGAN JD, SETLOW RB: Two forms of DNA repair in the DNA of human cells damaged by chemical carcinogens and mutagens. Cancer Res 34:3318-3325, 1974

(*5*) SETLOW RB, AHMED FE: DNA repair in human cells exposed to combinations of carcinogenic agents. *In* Carcinogenesis: Fundamental Mechanisms and Environmental Effects (Pullman B, Ts'o PO, Gelboin H, eds). Boston: Reidel, 1980, pp 453-464

(*6*) ARLETT CF, LEHMANN AR: Human disorders showing increased sensitivity to the induction of genetic damage. Annu Rev Genet 12:95-111, 1978

(*7*) SETLOW RB: DNA repair pathways. *In* DNA Repair and Mutagenesis in Eukaryotes (Generoso WM, Shelby MD, de Serres FJ, eds). New York: Plenum Press, 1980, pp 45-54

(*8*) HASELTINE WA, GORDON LK, LINDAN CP, et al: Cleavage of pyrimidine dimers in specific sequences by a pyrimidine dimer DNA-glycosylase of *M. luteus*. Nature 285:634-641, 1980

(*9*) DEMPLE B, LINN S: DNA N-glycosylase and DNA repair. Nature 287:203-208, 1980

(*10*) OLSSON M, LINDAHL T: Repair of alkylated DNA in *Escherichia coli*. Methyl group transfer from O^6-methylguanine to a protein cysteine residue. J Biol Chem 255:10569-10571, 1980

(11) AHMED FE, SETLOW RB: Kinetics of DNA repair in ultraviolet-irradiated and *N*-acetoxy-2-acetylaminofluo-

rene-treated mammalian cells. Biophys J 24:665–675, 1978

(*12*) Madden JJ, Falek A, Shafer DA, et al: Effects of opiates and demographic factors on DNA repair synthesis in human leukocytes. Proc Natl Acad Sci USA 76:5769–5773, 1979

(*13*) Harm W: Biological determination of the germicidal activity of sunlight. Radiat Res 40:63–69, 1969

(*14*) Setlow RB: The wavelengths in sunlight effective in producing skin cancer: A theoretical analysis. Proc Natl Acad Sci USA 71:3363–3366, 1974

(*15*) Scott EL, Straf ML: Ultraviolet radiation as a cause of cancer. *In* Origins of Human Cancer (Hiatt HH, Watson JD, Winsten JA, eds). Cold Spring Harbor, N.Y.: Cold Spring Harbor Laboratory, 1977, pp 529–546

(*16*) National Academy of Sciences: Protection against Depletion of Stratospheric Ozone by Chlorofluorocarbons. Washington, D.C.: Natl Acad Sci, 1979, pp 80–86

(*17*) Rundel RD, Nachtwey DS: Skin cancer and ultraviolet radiation. Photochem Photobiol 28:345–354, 1978

(*18*) Price GB, Modak SP, Makinodan T: Age-associated changes in the DNA of mouse tissue. Science 171:917–920, 1971

(*19*) Lindahl T: DNA glycosylases. *In* Chromosome Damage and DNA Repair (Seeberg E, Kleppe K, eds). New York: Plenum Press, 1982, pp 207–219

(*20*) Shapiro R: Damage to DNA caused by hydrolysis. *In* Chromosome Damage and DNA Repair (Seeberg E, Kleppe K, eds). New York: Plenum Press, 1982, pp 3–19

(*21*) Setlow RB, Setlow JK: Effects of radiation on polynucleotides. Annu Rev Biophys Bioeng 1:293–346, 1972

(*22*) Hart RW, Setlow RB: Correlation between deoxyribonucleic acid excision-repair and life-span in a number of mammalian species. Proc Natl Acad Sci USA 71:2169–2173, 1974

(*23*) Sutherland BM, Harber LC, Kochevar IE: Pyrimidine dimer formation and repair in human skin. Cancer Res 40:3181–3185, 1980

(*24*) Ley RD, Sedita BA, Grube DD, et al: Induction and persistence of pyrimidine dimers in the epidermal DNA of two strains of hairless mice. Cancer Res 37:3243–3248, 1977

(*25*) Paffenholz V: Correlation between DNA repair of embryonic fibroblasts and different life span of 3 inbred mouse strains. Mech Ageing Dev 7:131–150, 1978

(*26*) Hart RW, Sacher GA, Hoskins TA: DNA repair in a short- and a long-lived rodent species. J Gerontol 34:808–817, 1979

(*27*) Hart RW, Daniel FB: Genetic stability in vitro and in vivo. Adv Pathobiol 7:123–141, 1980

(*28*) Francis AA, Lee WH, Regan JD: The relationship of DNA excision repair of UV-induced lesions to the maximum life span of mammals. Mech Ageing Dev 16:181–189, 1981

(*29*) Kato H, Harada M, Tsuchoya K, et al: Absence of correlation between DNA repair in ultraviolet-irradiated mammalian cells and life span of donor species. Jpn J Genet 55:99–108, 1980

(*30*) Goldstein S: The role of DNA repair in aging of cultured fibroblasts from xeroderma pigmentosum and normals. Proc Soc Exp Biol Med 137:730–734, 1971

(*31*) Lambert B, Ringborg U, Skoog L: Age-related decrease of ultraviolet light-induced repair synthesis in human peripheral leukocytes. Cancer Res 39:2792–2795, 1979

(*32*) Woodhead AD, Setlow RB, Grist E: DNA repair and longevity in three species of cold-blooded vertebrates. Exp Gerontol 15:301–304, 1980

(*33*) Peleg L, Raz E, Ben-Ishai R: Changing capacity for DNA excision repair in mouse embryonic cells in vitro. Exp Cell Res 104:301–307, 1976

(*34*) Hart RW, Setlow RB: DNA repair in late-passage human cells. Mech Ageing Dev 5:67–77, 1976

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Repair deficient human disorders and cancer

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The analysis of the repair of damage to DNA in mammalian cells leads not only to a knowledge of which environmental agents are deleterious to living creatures, but also to an understanding of which reaction products in DNA are potentially carcinogenic and which tissues are the more sensitive.

In a number of recessively inherited human disorders, the affected individuals are cancer prone[1]. The prevalence of cancer among such individuals ranges from significantly higher to orders of magnitude higher than in the general population[2-4]. Three of these disorders—xeroderma pigmentosum (XP), ataxia telangiectasia (AT) and Fanconi's anaemia (FA)—are associated with defects in the ability of cells to repair certain kinds of physical or chemical damage to their DNA. The existence of such disorders is direct evidence that damage to DNA can be carcinogenic, and is the best available evidence for a causal association between mutagenic and carcinogenic agents—an association used extensively as an environmental detection screen for carcinogens[5]. The support for the causal connection is further strengthened by the observation that mutations occur in XP cells at lower doses of carcinogens than those affecting normal cells[6].

The clinical symptoms of the disorders are completely different, as are the known defects in repair. XP is characterised by the extreme sensitivity of skin to sunlight[3,4,7]; AT by progressive cerebellar ataxia and dilated blood vessels in the eye, as well as immune deficiencies[2]; and FA by haematological abnormalities that ultimately lead to death as a result of haemorrhage or haematological failure[4]. FA may also include various skeletal deformities. The diseases are rare, approximately one in several hundred thousand births, but heterozygotes are estimated to be one in several hundred[8]. However, heterozygotes do not show indications of the disorders and are not cancer prone, except in FA for which there is evidence of a higher risk of leukaemia. It has been estimated that 5% of all individuals dying of acute leukaemia are FA heterozygotes[8]. Thus, although the diseases are not general public health problems, analysis of the molecular defects in them should elucidate the molecular nature of the changes responsible for killing, mutagenesis and carcinogenesis, and give estimates of the probability that such changes result in biological effects. Since human risks can only be assessed from data on molecules and animals extrapolated to humans, usually by means of scanty epidemiological data, it is important that we have an understanding of the molecular mechanisms involved so as to provide a theoretical base for the extrapolations. Such a long-range, seductive goal has lead to a wide range of investigations on the association of repair defects with other human conditions, including ageing and high blood pressure.

Almost all our notions about the molecular nature of repair come from studies on bacterial systems because of the large number of genetically well defined repair-deficient mutants and the relative ease in analysing photochemical and molecular changes in them[9,10]. The genetic analysis of repair in mammalian systems is based on the naturally occurring human inherited diseases. The concepts are simple but the problems are complex because physical or chemical agents make more than one change in DNA and there is no reason to assume that the changes have large biological consequences in normal cells. If a particular product is repaired well in normal cells and not in sensitive ones, it may be that the product is bad for the latter but innocuous for the former. Moreover, if a product is not repaired in both normal and sensitive cells, one cannot assume without other information that it has any biological effect. For ultraviolet radiation there are experimental tricks that permit one to show that pyrimidine dimers alter the biological function of DNA and affect both sensitive and resistant cells, even though the latter are highly proficient in excising dimers. The trick is to use the fact that photoreactivating (PR) enzymes in the presence of light are able to break pyrimidine dimers into monomers without affecting any other known photoproduct[9]. Hence, if ultraviolet (UV) affects some biological function and the effect of ultraviolet is ameliorated by subsequent exposure to PR light, one can assume that the initial biological effect arose from dimers in DNA. Such a conclusion does not indicate the molecular mechanisms by which dimers produce their effects. They could be the induction of viruses, changes in transcription or inhibition of repair of other products. The identification of dimers as inactivating transforming DNA, killing and causing mutations in bacteria, transforming fish cells, and inhibiting DNA synthesis in human cells means that ultraviolet is the best understood model for environmental carcinogenesis[9,11,12].

Excision defective XP cells seem to be analogues of the *uvrAB* mutants of *E. coli*. However, details of excision in *E. coli* are not well known because even though the *uvrAB* endonuclease makes single-strand nicks in UV-irradiated DNA, one can easily calculate from published data[13] that the number of nicks are many-fold fewer than the numbers of dimers. Hence, the action of the endonuclease *in vitro* seems to be on minor photoproducts in DNA. Similar conclusions are reached about most of the UV endonucleases that have been isolated from prokaryotic or eukaryotic systems. Exceptions are those isolated from *M. luteus* and from T4 phage infected *E. coli*[9,10]. It is no wonder that the details of repair of UV damage in human cells, where in XP there are at least five complementation groups[7], are not known.

Types of repair

The existence of cell strains sensitive to certain environmental agents does not imply that the sensitivity arises from a defect in repair unless one can show that the initial deleterious products occur in similar numbers in both sensitive and resistant cells. But this demonstration requires a knowledge—usually incomplete—of what the products are. Hence, the best way to assess the role of repair is to measure host cell reactivation—

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the ability of cells to affect the survival of viruses treated with chemical or physical agents outside the cell. Low survival is interpreted as a defect in repair. The technique is applicable to unknown types of damage and to unknown types of repair system.

The direct measurement of excision repair requires determination of loss from DNA of products that have biological consequences. It is this latter aspect of the problem that has led to the emphasis on pyrimidine dimers in DNA[9-14]. In subsequent experiments one can use indirect measures of repair such as unscheduled DNA synthesis, repair replication or the photolysis of incorporated BUdR[9-14]. These techniques can be used as measures of DNA repair even though they do not identify uniquely what change is repaired or the changes that are biologically important. However, defective repair may not be readily apparent because a product of little biological consequence may well be repaired whereas a minor product with important biological consequences is not well repaired. This seems to be the case for alkylation damage to DNA. Both normal and XP cells are able to remove readily N^7-alkylGua, but only normal cells can do it for the minor product O^6-alkylGua[15]. Nevertheless, the various measures of excision repair usually give similar results. In cells with a low level of excision repair for dimers, repair replication is not necessarily an adequate measure of dimer excision because, presumably, repair replication also detects repair of minor photoproducts.

At a mean lethal ultraviolet dose to excision-defective cells there are many dimers per cell[9]. Hence, cells have evolved effective ways of bypassing alterations to their DNA. In both bacterial and mammalian systems the DNA made on a damaged template is often smaller than that made on undamaged ones[16]. The small DNA is subsequently chased into pieces the size of the parent, and the process of chasing the small DNA into large is called post-replication repair. In a number of instances the size of the small DNA is compatible with the idea that pyrimidine dimers act as blocks to synthesis, and this notion is reinforced by the observation that PR treatment before the pulse label results in much larger DNA in bacterial, marsupial, and chicken cells[16]; in all of which PR illumination breaks dimers into monomers. In bacteria the new DNA acts as if it contains gaps and the gaps are filled in by exchanges between parental and daughter DNA. Post-replication repair is defective in rec$^-$ and lex$^-$ mutants of *E. coli* and in such cells susceptibility to mutation by UV radiation is also greatly reduced[17]. These and other arguments have led to the notion that at least a part of post-replication repair in *E. coli* is inducible by small doses and such doses induce a new protein, the so-called protein X[17]. The appearance of this new protein is associated with the fixation of mutations.

It is reasonable to carry over these ideas to mammalian cells but the molecular mechanism involved in post-replication repair in mammals is in dispute. In some experiments the newly synthesised DNA acts as if it contains gaps that are filled in during post-replication repair and the gaps were estimated to be about 1,000 nucleotides long[18], although more recent estimates put the number closer to 200 (R. B. S. and E. Grist, unpublished). There seem to be comparatively few exchanges[18] and the evidence for the existence of gaps in the newly replicated DNA comes only from experiments on the photolysis of DNA repaired in the presence of BUdR. Synthesis may take place by a replicative bypass mechanism[19,20] without production of gaps and there is evidence that the gaps, if any, are not opposite the dimers in the parental DNA[21-23]. Perhaps both modes of synthesis take place. Post-replication repair is defective in XP variants but it can be speeded up by pretreatment of cells with small doses of ultraviolet or *N*-acetoxy-AAF[24,25]. The role, if any, of this enhanced repair is not clear. It takes place not only after split doses but also with single doses (R. B. S. and E. Grist, unpublished). The role of post-replication repair in mutagenesis can be identified in bacteria because it is possible to remove the lesions at known times by PR treatment[17]. Such a technique has not been developed for mammalian cells. It is an intriguing observation that protease inhibitors that block the induced repair functions in *E. coli* also acts as inhibitor of tumour promotion[26].

Defective excision or post-replication repair does not seem to be involved in the formation of spontaneous sister chromatid exchanges since various XP cell lines show no significant differences from normal cells[27]. However, treated, excision defective XP cells always show more sister chromatid exchanges independent of the repair capability of the cells for the major product of the chemical agent[27]. Hence, the main chemical damage detected as affecting DNA is not necessarily that responsible for chromosomal effects, although for ultraviolet the PR of chromosome aberrations in marsupial cells indicates that pyrimidine dimers are important[28]. In any event increases in chromosome aberrations are correlated with decreases in excision repair, although sister chromatid exchanges are not[29].

Xeroderma pigmentosum

Xeroderma pigmentosum is the most widely studied repair-deficient human disease[7]. Affected individuals develop light-induced skin cancer with a prevalence among whites at age 20, of approximately 100%—a value at least 10^3-fold greater than for the general population[30]. All XP cells are defective in at least one mode of repair of ultraviolet damage to DNA. Most XP individuals have a defect in the excision repair pathway for ultraviolet damage. The defect is not complete, but may be over 90% in some individuals and only 50% in others[7]. Although few quantitative comparisons of repair kinetics have been made by one laboratory using several methods, it is comforting that similar estimates of the extent of excision defects are found by a number of different techniques, such as cell survival and mutation after irradiation[6], ability to reactivate ultraviolet inactivated viruses[31], the loss of dimers from DNA[14], loss of ultraviolet endonuclease sensitive sites[32], unscheduled DNA synthesis[7], and repair replication[16] either by direct observation or by the photolysis of incorporated BUdR. Among the excision-defective individuals there is a good correlation between the severity of the molecular defect and the severity of the disease[33], although the latter also must depend on the exposure to the deleterious wavelengths in sunlight. The fact that the mutation frequency per unit dose is higher in these XP cells, but that the frequency at a given survival is the same for normals is a biological indication that excision repair is error-free[6]. Biochemical and biophysical data indicate also that excision repair makes no large errors[34].

The defect in excision seems to be associated with a malfunction of the incision step during incubation after UV irradiation of XP cells, since only small numbers of single strand breaks are observed compared with the numbers of dimers in DNA[14,35]. Moreover, when T4 endonuclease is introduced into irradiated XP cells, unscheduled DNA synthesis approaching normal levels is observed and the introduced enzyme increases cell survival[36]. Excision defective cells fall into five complementation groups[7]. Hybrids of any two are close to normal in unscheduled synthesis, repair replication and loss of sites sensitive to ultraviolet endonuclease, as well as by the ability of such heterokaryons to reactivate ultraviolet irradiated viruses. One might think that active endonuclease is formed in the heterokaryons from diffusible parts of inactive multimeric enzymes. However, sonicates of XP cells are able to excise dimers from exogenous DNA but are not able to excise dimers from their own chromatin, whereas normal cells are[37]. Thus, the nature of the molecular defect in XP cells is not known.

A sixth group of xeroderma pigmentosum individuals is proficient in excision repair. The existence of these individuals was an important exception to the association between the severity of repair defect and the severity of the disorder. However, cells of this group are now known to be defective in post-replication repair[38], are more sensitive to ultraviolet radiation[6], and are not fully proficient in host cell reactivation[39]. Moreover; not only the mutation frequency at a given dose, but the mutation frequency at a given survival is higher than that of normal cells, implying that some steps in repair of XP variant cells are more error-prone than in normal or in conventional XP cells[39].

The experiments summarised above use acute exposures of cells to 254 nm radiation at doses of 1–20 J m^{-2}. People receive much smaller equivalent doses per exposure. One minute exposure to the noon sun in Texas in September would be equivalent to approximately 0.1 J m^{-2} of 254 nm[40] and the amount transmitted through the upper inert layer of skin would be closer to 0.01 J m^{-2}. Hence, the actual carcinogenic environment is a far cry from the experiments done in the laboratory. Moreover people are exposed to strong visible light at the same time that they are exposed to ultraviolet. Human cells have PR enzyme activity and XP cells in culture have less activity than do normals[41]. Although the enzymatic activity of cells in culture depends upon the culture medium[42], it is reasonable to suppose that the enzyme would act *in vivo* and that the number of dimers in cells would be determined by the relative levels of ultraviolet and visible radiation and the PR and excision enzymes. It is intriguing that in all the XP cell lines investigated the sum of the three repair activities: excision, post-replication, and PR is about one half of normal[41].

The fact that all XP cell lines are defective in one or more repair pathway for UV damage makes it attractive to speculate[44] that UV-induced skin carcinogenesis in normal human-beings has a low probability because most of the lesions are removed and DNA synthesis beyond any that remain is relatively error free. In excision defective XP cells many dimers remain and replication beyond them, although relatively error free, makes an appreciable number of mistakes and hence gives a high possibility for neoplastic transformation. In the XP variants there are a few more dimers than in normals because of a defect in PR, but replication beyond dimers is error prone and, as in the case of conventional XPs, an appreciable number of mistakes is made. Similar speculations have been made for chemical damage[43].

From ultraviolet to chemicals

Bacteria that are defective in repairing ultraviolet damage are also defective in repairing a number of other damages to DNA, for example, nitrogen mustard, 4-NQO, and the effects of black-light plus psoralen[6,44]. Hence it is not surprising that the same is true for XP cells, and the repair of damaged DNA is more general than just the special case of repair of pyrimidine dimers. There are several damaging agents that are repaired effectively in XP cells[45–49]. Such damage results from ionising radiation, the photolysis of BUdR and the action of simple alkylating agents. Repair in these cases involves both the repair of single strand breaks and probably excision repair mediated by *N*-glycosidases[10] or by spontaneous base removal followed by the action of an apurinic endonuclease[10]. However, apurinic endonuclease isolated from XP cells shows changes when compared with the normal enzyme[49]. The classification of chemical agents as making reparable or irreparable damage in XP cells is useful but not unique because a number of different products may be formed from a single agent. For example, alkylation of DNA affects many groups. The N^7-alkylGua is removed efficiently in XP cells but the O^6-alkylGua is not[15]. Table 1 lists agents and products in terms of their repair by XP, AT, and FA cells. In the small number of cases that have been investigated carefully the sizes of the patches for agents repaired effectively by normal cells, but not by XP cells have been measured. The patches are large (30–100 nucleotides) and they are an order of magnitude larger than the number of bases inserted during repair of single strand breaks[46–48].

The simplicity of the above picture is deceptive. One might suppose that the compounds mimicking ultraviolet would be acted upon by common repair pathways since the rate-limiting step in their repair is considered to be the initial endonucleolysis (see above). However, acetylaminofluorene-(AAF) and ultraviolet-induced damage do not compete for this putative common step. AAF treatment of normal human cells does not inhibit dimer excision at ultraviolet doses that saturate the excision pathway[49]. Thus, our molecular picture of excision is far from complete. Nevertheless, agents that mimic the ultraviolet effect of excision also mimic its effects on cell survival and mutagenesis[6,7] and in post replication repair. Moreover, in XP variants post-replication repair after ultraviolet or AAF is enhanced by treatment of the cells several hours earlier with small doses of either ultraviolet or AAF[21,28].

Repair in transformed or differentiated cells

As a general rule proficiency in repair of physical or chemical damage to DNA is independent of the cell type or tissue of origin. For example, transformation of cells by SV40 virus does not affect the ability or inability to repair ultraviolet damage[7] and all tissues tested from XP individuals[3,70], including melanoma cells, are as defective in repair as are fibroblasts or lymphocytes. Moreover, tissues from non-XP individuals repair ultraviolet damage whether the tissues represent material from spontaneous tumours or normal tissue[70]. Nevertheless, repair does not seem to be uniformly distributed over the chromosomes or throughout chromatin[71,72].

There are important exceptions to the above generalisation: (1) lymphocytes stimulated by concanavalin A are 10-fold more proficient in unscheduled DNA synthesis after AAF treatment than are unstimulated lymphocytes[73]. It was concluded that the rate of excision is a function of the capacity for DNA synthesis and that unstimulated lymphocytes cannot readily be used to distinguish repair arising from agents that give rise to long patch repair from those that give rise to short patch repair. (2) Some melanoma cells are very resistant in culture and resistance is not associated with a lower yield of ultraviolet induced dimers nor with an increase in the rates of excision or post-replication repair[74]. (3) Mouse fibroblasts are defective in excision repair of ultraviolet damage[46,75] and so are epithelial cells in mouse skin[76]. (The interpretation in an earlier report[77] of excision of mouse skin is confounded by the high surface, but low average, dose of 254 nm.) However, early passage cells from 13–15-d-old mouse embryos excise dimers from DNA into the acid soluble fraction of the nucleus[78]. Cells from passages greater than 7 cannot do this nor can early passage cells from 17-19-d-old embryos. The latter are like cells from adult animals or most rodent cells in culture in that they do little excision repair of pyrimidine dimers. Similarly, after UV irradiation myocardial cells from newborn rats show extensive unscheduled DNA synthesis compared with cells from 3–12-month-old animals[79]. These findings raise the possibility that the mutations leading to the XP phenotype are not in structural genes for proteins involved in excision repair, but are alterations in control elements that result in shutting off portions of repair pathways.

Ataxia telangiectasia

The association between exposure to sunlight and high prevalence of skin cancer in XP made it relatively easy to relate the disease to defects in repair of ultraviolet damage, expecially since there were good hints from prokaryotes that pyrimidine dimers were typical lesions to be investigated. AT is more difficult to understand at the molecular level because cancer in this disease has not been associated with a particular environmental agent. The realisation that AT individuals are sensitive to X rays (see ref. 60), and that their levels of spontaneous and radiation induced chromosome aberrations are increased[60] led to the demonstration that fibroblasts from affected individuals are 3–4-fold more sensitive to X rays than normal cells[60]. AT cells are proficient in the repair of ultraviolet[61,64] and AAF damage[65]. The main biological effects of X rays are thought to be base damage—perhaps double-strand breaks[6].

All the AT cell lines investigated are proficient in the repair of single- and double-strand breaks[40-43]. However, 6 out of 12 lines are defective in repair replication following anoxic irradiation[43]. (Anoxic radiation enhances the proportion of base damage to single-strand breaks.) Four of the cell lines showed normal repair replication. Hence, AT is genetically heterogeneous as is XP. Among three of the repair defective cell lines, fusion studies showed that there were two complementation groups[43].

Table 1 Damaging agents or products for which cells are repair proficient or deficient

Proficient	Deficient
Xeroderma pigmentosum	
Ionising radiation —strand breaks —anoxic 4—NQO (minor comp) NO—carbaryl[44] NO—Me guanidine MNNG MMS MNU EMS N^7-alkylGua Proflavin—light[44] Mitomycin C[33]	Ultraviolet —dimers —protein DNA links[40] —strand breaks[41] Ionising radiation—anoxic 4—NQO AAF damage ICR—170 Aflatoxin K—region epoxides[4] Br benzanthracene Br, Me benzanthracene[43] EMS O^6-alkylGua Psoralen—light[44] Chlorpromazine—light[46] BCNU HNO_2[47] Propane sultone Decarbamyl mito C[33]
Ataxia telangectasia	
Ionising radiation —strand breaks[40-44] —endonuclease sites[48] Mitomycin C[38] MMS[38] Ultraviolet[44] AAF—damage[4]	Ionising radiation —chromosomes[4] —survival[38] —endonuclease sites[43] Actinomycin D[44] Mitomycin C MMS
Fanconi's anaemia[46]	
Decarbamyl mito C MNNG 4—NQO MMS Ultraviolet	Mitomycin C Psoralen—light HN_2 DNA crosslinks γ-rays[47] Ultraviolet (high dose)[48]

Cells are categorised on the basis of survival, host cell reactivation, or by chromosomal, biochemical or biophysical measures of repair. (A listing in both catagories means that there are several products of an agent or that all cell lines are not the same. In addition to specific references consult the text and refs 7, 14, 45–48.)

A protein extract from *M. luteus* makes single-strand breaks in DNA X ray-irradiated *in vivo* or *in vitro*. The extract can be used to determine whether such nuclease sensitive sites are removed from DNA during incubation following irradiation. Two cell lines defective in repair replication were assessed by this technique and were found to remove endonuclease sensitive sites at a much slower rate than normal cells[43]. The nature of the alteration that is not excised is unknown. It could be thymidine damage of the hydroxy hydroperoxide type even though such damage is removed readily from exogenous DNA by cell sonicates of repair defective cells[40] because, as in the case of pyrimidine dimers and XP sonicates[37], such sonicates might not mimic conditions *in vivo*.

The repair defects in AT are not confined to X rays but include chemical damages as well (see Table 1). Hence, there is a strong possibility of identifying the molecular nature of some of the damages repaired poorly in AT and perhaps estimating whether there are particular environmental hazards associated with the initiation of cancer in this disease.

Fanconi's anaemia

A genetic analysis indicates that the defect is heterogeneous[41]. Cells from affected individuals show more spontaneous chromosome aberrations than do normal ones[49], and treatment of cells with DNA cross-linking agents such as nitrogen mustard, mitomycin C, or psoralen plus black light gives rise to 30-fold more chromosomal aberrations than observed in treated normal cells[46]. Monofunctional agents do not give rise to such a big difference although the number resulting from UV irradiation is approximately fivefold more than in normal cells[46]. These data are interpreted as indicating that FA cells have a defect in the repair of cross links[46]. On the other hand treatment with mitomycin C results in a decrease in the numbers of sister chromatid exchanges[43].

FA cells are appreciably more sensitive to killing my mitomycin C than are HeLa or XP cells and their DNA, analysed on alkaline gradients immediately after treatment, sediments more rapidly than DNA from untreated cells[34]. At 4 h after treatment more of the DNA is larger than immediately after treatment. These data indicate that cross linking reactions take place after treatment. In normal or XP cells treated with mitomycin C a decrease in molecular weight is observed immediately after treatment, and in several hours the size of the DNA from treated cells returns to normal. The pattern of changes is as if an endonuclease breaks the affected DNA and repair is completed by excision, polymerisation and ligation. The repair of mitomycin C damage seems to be by pathways different from that of ultraviolet damage since cells that repair such damage show few strand breaks during repair[44-38].

FA cells may also be slightly defective in the repair of γ-ray and ultraviolet damage. γ-irradiated adenovirus does not grow as well on FA cells and, at high doses, ultraviolet irradiated virus does not grow as well as on normals[47]. At high doses, but not low, the excision repair of γ-ray products or of pyrimidine dimers seems defective[48]. However, as for all cells investigated to date, the repair of single strand breaks is not deficient, but in cell homogenates, the ability to remove high doses of t' from exogenous DNA is defective in two of four cell lines investigated[43].

Bloom's syndrome

A repair deficiency is inferred from the finding of large numbers of spontaneous chromosomal aberrations and well over a 10-fold increase in sister chromatid exchanges in untreated lymphocytes[1,38,44]. Lymphocytes from some individuals have a bimodal distribution of the sister chromatid exchanges[44]. This finding suggests that the syndrome results from changes at a regulatory rather than a structural locus. The dimorphism is not observed in fibroblast or bone marrow cells. The chromosomes are more sensitive to radiation[38] and the cells are slightly more sensitive to ultraviolet[46]. The rate of fork motion during DNA replication is slower than normal in Bloom's syndrome[44] and might account for the observation that the sedimentation of pulse labelled DNA after UV irradiation is somewhat slower than in normal cells[46].

Other human diseases and conditions

The successes in correlating some diseases causing cancer proneness with defects in DNA repair have lead to searches for other repair deficient diseases. Light sensitive diseases other than XP have not been found to be defective in excision of ultraviolet damage[17]. However, individuals with actinic keratoses—a potential precarcinogenic condition—have slightly decreased levels of unscheduled synthesis[48], and high blood pressure has been associated with a decrease in repair and an increase in chromosomal aberrations in lymphocytes treated with AAF[89]. The cells of Cockayne's syndrome are reported to be ultraviolet sensitive, but the molecular defect is not known[90].

The screening of cells for X ray-sensitivity has indicated that cells of D-type retinoblastoma individuals are more X ray-sensitive than normals or those of familial retinoblastoma[91]. On the other hand fibroblasts from four individuals with abnormal responses to X rays have normal survival curves and normal repair of single strand breaks[92].

Two general types of experiment have been done in attempts to correlate ageing with changes in DNA repair. In the first the repair capabilities of young and old cells in culture were compared and in the second cells with syndromes of premature ageing were investigated. Both gave somewhat equivocal results. Cells from some progeroid individuals were reported to be defective in the repair of single-strand breaks arising from ionising radiation[93], but other investigators have not been able to obtain these results[94,95], and chromosome breakage is not abnormally sensitive in these cells[96]. However, measurements of the ability of γ-ray irradiated adenovirus to grow on progeroid cells indicates that they do have some deficiency[97].

Late passage cultures may or may not show reduced capacities to repair damages of various types[98-100] but the reduction, at least for ultraviolet damage, is not uniformly distributed among cells[100]. Cells that do not go through the cell cycle do not do appreciable unscheduled synthesis, but late passage cells that do cycle do repair. Hence, there is no evidence that a defect in repair leads to senescence. It might be a consequence of it. I interpret the intriguing correlation between DNA repair in ultraviolet irradiated cells in culture and the life span of the donor animal[75] not as indicating a casual relation between life span and repair, but a consequence of the turning off of parts of the repair system at early ages in the development of some animals.

Conclusion

Cells from most individuals are proficient in the repair of DNA damage. Retrospective studies have shown that individuals defective in repair are cancer prone and our knowledge of the molecular nature of the defects leads to the strong prediction that unrepaired damage to DNA has a high carcinogenic potential. The complexity of carcinogenesis, on the other hand, also indicates that not all cancers arise from defects in repair. Nevertheless, even in normal individuals the rate of DNA repair compared with other cellular processes should be an important parameter in the initial steps in carcinogenesis. Hence, an understanding of the control and kinetics of repair processes is as important as a knowledge of the activation and inactivation pathways for chemical carcinogens in extrapolations of carcinogenic hazards to humans.

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1. German, J. *Progr. Med. Genet.* 8, 61–101 (1972).
2. Harnden, D. G. in *Chromosomes and Cancer* (ed. German, J.) 619–636 (Wiley, New York, 1974).
3. Robbins, J. H., Kraemer, K. H., Lutzner, M. A., Festoff, B. W. & Coon, H. G. *Annls int. Med.* 80, 221–248 (1974).
4. Takebe, H. *et al. Cancer Res.* 37, 490–495 (1977).
5. Bridges, B. A. *Nature* 261, 195–200 (1976).
6. Maher, V. W. & McCormick, J. J. in *Biology of Radiation Carcinogenesis* (eds Yuhas, J. M., Tennant, R. W. & Regan, J. D.) 129–145 (Raven, New York, 1976).
7. Cleaver, J. E. & Bootsma, D. *A. Rev. Genet.* 9, 19–38 (1975).
8. Swift, M. *Nature* 230, 370–373 (1971).
9. Setlow, R. B. & Setlow, J. K. *A. Rev. Biophys. Bioengng* 1, 293–346 (1972).
10. Grossman, L., Braun, A., Feldberg, R. & Mahler, I. *A. Rev. Biochem.* 44, 19–43 (1975).
11. Hart, R. W., Setlow, R. B. & Woodhead, A. D. *Proc. natn. Acad. Sci. U.S.A.* (in the press).
12. Sutherland, B. M. & Oliver, R. *Mutat. Res.* 46, 159–160 (1977).
13. Braun, A., Radman, M. & Grossman, L. *Biochemistry* 15, 4116–4120 (1976).
14. Cleaver, J. E. *Adv. Radiat. Biol.* 4, 1–75 (1974).
15. Goth-Goldstein, R. *Nature* 267, 81–82 (1977).
16. Lehmann, A. R. *Life Sci.* 15, 2005–2016 (1975).
17. Witkin, E. *Bact. Rev.* 40, 869–907 (1976).
18. Waters, R. & Regan, J. D. *Biochem. biophys. Res. Commun.* 72, 803–807 (1976).
19. Higgins, N. P., Kato, K. & Strauss, B. *J. molec. Biol.* 101, 417–425 (1976).
20. Fujiwara, Y. & Tatsumi, M. *Mutat. Res.* 37, 91–110 (1976).
21. Meneghini, R. & Hanawalt, P. C. *Biochim. biophys. Acta* 425, 428–437 (1976).
22. Clarkson, J. M. & Hewitt, R. R. *Biophys. J.* 16, 1155–1164 (1976).
23. Lehmann, A. R., Kirk-Bell, S., Arlett, C. F., Harcourt, S. A., de Weerd-Kastelein, E. A., Keijzer, W. & Hall-Smith, P. *Cancer Res.* 37, 904–910 (1977).
24. Setlow, R. B., Ahmed, F. E. & Grist, E. in *Origins of Human Cancer* (eds Hiatt, H. H., Watson, J. D. & Winsten, J. A.) (Cold Spring Harbor Laboratory, New York, in the press).
25. D'Ambrosio, S. M. & Setlow, R. B. *Fedn Proc.* 36, 848 (1977).
26. Meyn, S., Rossman, T. & Troll, W. *Proc. natn. Acad. Sci. U.S.A.* 74, 1152–1156 (1977).
27. Wolff, S., Rodin, B. & Cleaver, J. E. *Nature* 265, 347–349 (1977).
28. Griggs, H. G. & Bender, M. A. *Photochem. Photobiol.* 15, 517–526 (1972).
29. Parrington, J. M., Delhanty, J. D. A. & Baden, H. P. *Ann. hum. Genet.* 35, 149–160 (1971).
30. Scott, E. L. & Straf, M. L. in *Origins of Human Cancer* (eds Hiatt, H. H., Watson, J. D. & Winsten, J. A.) (Cold Spring Harbor Laboratory, New York, in the Press).
31. Day, R. S. III *Cancer Res.* 34, 1965–1970 (1974).
32. Paterson, M. C., Lohmann, P. H. M. & Sluyter, M. L. *Mutat. Res.* 19, 245–256 (1973).
33. Bootsma, D. in *Research in Photobiology* (ed. Castellani, A.) 455–468 (Plenum, New York, 1977).
34. Lieberman, M. W. *Int. Rev. Cytol.* 45, 1–23 (1976).
35. Fornace, A. J. Jr., Kohn, K. W. & Kann, H. E. Jr *Proc. natn. Acad. Sci. U.S.A.* 73, 39–43 (1976).
36. Tanaka, K., Hayakawa, H., Sekiguchi, M. & Okada, Y. *Proc. natn. Acad. Sci. U.S.A.* 74, 2958–2962 (1977).
37. Mortelmans, K., Friedberg, E. C., Slor, H., Thomas, G. & Cleaver, J. E. *Proc. natn. Acad. Sci. U.S.A.* 73, 2757–2761 (1976).
38. Day, R. S. *Nature* 253, 748–749 (1975).
39. Maher, V. M., Ouellette, L. M., Curren, R. D. & McCormick, J. J. *Nature* 261, 593–595 (1976).
40. Harm, W. *Radiat. Res.* 40, 63–69 (1969).
41. Sutherland, B. M. & Oliver, R. *Nature* 257, 132–134 (1975).
42. Sutherland, B. M. & Oliver, R. *Biochim. biophys. Acta* 442, 358–367 (1976).
43. Kondo, S. *Br. J. Cancer* 35, 595–601 (1977).
44. Nagao, M. & Sugimura, T. *Adv. Cancer Res.* 23, 131–169 (1976).
45. Stich, H. F. in *Origins of Human Cancer* (eds Hiatt, H. H., Watson, J. D. & Winsten, J. A.) (Cold Spring Harbor Laboratory, New York, in the press).
46. Cleaver, J. E. *Cancer Res.* 33, 362–369 (1973).
47. Regan, J. D. & Setlow, R. B. *Cancer Res.* 34, 3318–3325 (1974).
48. Regan, J. D. & Setlow, R. B. in *Biology of Radiation Carcinogenesis* (eds Yuhas, J. M., Tennant, R. W. & Regan, J. D.) 103–113 (Raven, New York, 1976).
49. Kuhnlein, Y., Penhoet, E. E. & Linn, S. *Proc. natn. Acad. Sci. U.S.A.* 73, 1169–1173 (1976).
50. Fornace, A. J. Jr & Kohn, K. W. *Biochim. biophys. Acta* 435, 95–103 (1976).
51. Dingman, C. W. & Kakunaga, T. *Int. J. Radiat. Biol.* 30, 55–66 (1976).
52. Regan, J. D., Setlow, R. B., Francis, A. A. & Lijinsky, W. *Mutat. Res.* 38, 293–302 (1976).
53. Lieberman, M. W. & Poirier, M. C. *Cancer Res.* 33, 2097–2103 (1973).
54. Regan, J. D. & Setlow, R. B. *Photochem. Photobiol.* 23, 345–346 (1976).
55. Day, R. S. III, Giuffrida, A. S. & Dingman, C. W. *Mutat. Res.* 33, 311–320 (1975).
56. Day, R. S. III & Dimattina, M. *Chem.-Biol. Interact.* 17, 89–97 (1977).
57. Day, R. S. III *Mutat. Res.* 27, 407–409 (1975).
58. Fujiwara, Y., Tatsumi, M. & Sasaki, M. S. *J. molec. Biol.* 113, 635–649 (1977).
59. Higurashi, M. & Cohen, P. E. *Cancer* 32, 380–383 (1973).
60. Taylor, A. M. R. *et al. Nature* 258, 427–429 (1975).
61. Lehmann, A. R. & Stevens, S. *Biochim. biophys. Acta* 474, 49–60 (1977).
62. Paterson, M. C., Smith, B. P., Knight, P. A. & Anderson, A. K. in *Research in Photobiology* (ed. Castellani, A.) 207–218 (Plenum, New York, 1977).
63. Hoar, D. I. & Sargent, P. *Nature* 261, 590–592 (1976).
64. Arlett, C. F. *Mutat. Res.* 46, 106 (1977).
65. Amacher, D. E. & Lieberman, M. W. *Biochem. biophys. Res. Commun.* 74, 285–290 (1977).
66. Sasaki, M. S. & Tonomura, A. *Cancer Res.* 33, 1829–1836 (1973).
67. Rainbow, A. J. & Howes, M. *Int. J. Radiat. Biol.* 31, 191–195 (1977).
68. Poon, P. K., O'Brien, R. L. & Parker, J. W. *Nature* 250, 223–225 (1974).
69. Ahmed F. E. & Setlow, R. B. *Proc. natn. Acad. Sci. U.S.A.* 74, 1548–1552 (1977).
70. Newsome, D. A., Kraemer, K. H. & Robbins, J. H. *Archs Ophthalmol.* 93, 660–662 (1975).
71. Berliner, J., Mello, R. S. & Norman, A. *Radiat. Res.* 68, 509–513 (1976).
72. Wilkins, R. J. & Hart, R. W. *Nature* 247, 35–36 (1974).
73. Scudiero, D., Norin, A., Karran, P. & Strauss, B. *Cancer Res.* 36, 1397–1403 (1976).
74. Chalmers, A. H., Lavin, M., Atisoontornkul, S., Mansbridge, J. & Kidson, C. *Cancer Res.* 36, 1930–1934 (1976).
75. Hart, R. W. & Setlow, R. B. *Proc. natn. Acad. Sci. U.S.A.* 71, 2169–2173 (1974).
76. Ley, R. D., Sedita, B. A., Grube, D. D. & Fry, R. J. M. *Cancer Res.* 37, 3243–3248 (1977).
77. Bowden, G. T., Trosko, J. E., Shapas, B. G. & Boutwell, R. K. *Cancer Res.* 35, 3599–3607 (1975).
78. Peleg, L., Raz, E. & Ben-Ishai, R. *Expl Cell Res.* 104, 301–307 (1976).
79. Lampidis, J. J. & Shaiberger, G. E. *Expl Cell Res.* 96, 412–416 (1975).
80. Remsen, J. F. & Cerutti, P. A. *Mutat. Res.* 43, 139–146 (1977).
81. Schroeder, T. M., Tilgen, D., Kruger, J. & Vogel, F. *Hum. Genet.* 32, 257–288 (1976).
82. Latt, S. A., Stetten, G., Juergens, L. A., Buchanan, G. R. & Gerlad, P.S. *Proc. natn. Acad. Sci. U.S.A.* 72, 4066–4070 (1975).
83. Remsen, J. F. & Cerutti, P. A. *Proc. natn. Acad. Sci. U.S.A.* 73, 2419–2248 (1976).
84. German, J., Schonberg, S., Louie, E. & Chaganti, R. S. K. *Am. J. hum. Genet.* 29, 248–255 (1977).
85. Gianelli, F., Benson, P. F., Pawsey, S. A. & Polani, P. E. *Nature* 265, 466–469 (1977).
86. Hand, H. & German, J. *Proc. natn. Acad. Sci. U.S.A.* 72, 758–762 (1975).
87. Cleaver, J. E. *J. invest. Dermatol.* 54, 181–195 (1970).
88. Lambert, B., Ringborg, U. & Swanbeck, J. *J. invest. Dermatol.* 67, 594–598 (1976).
89. Pero, R. W., Bryngelsson, C., Mitelman, F., Thulin, T. & Norden, A. *Proc. natn. Acad. Sci. U.S.A.* 73, 2496–2500 (1976).
90. Wade, M. H., Chu, E. H. Y. & Schmickel, R. D. *Mutat. Res.* 46, 50 (1977).
91. Weichselbaum, R. R., Nove, J. & Little, J. B. *Nature* 266, 726–727 (1977).
92. Weichselbaum, R. R., Epstein, J. & Little, J. B. *Radiology* 121, 479–482 (1976).
93. Epstein, J., Williams, J. R. & Little, J. B. *Proc. natn. Acad. Sci. U.S.A.* 70, 977–981 (1973).
94. Regan, J. D. & Setlow, R. B. *Biochem. biophys. Res. Commun.* 59, 858–864 (1974).
95. Bradley, M. O., Erickson, L. C. & Kohn, K. W. *Mutat. Res.* 37, 279–292 (1976).
96. Bender, M. A. & Rary, J. M. *Radiat. Res.* 59, 181 (1974).
97. Rainbow, A. H. & Howes, M. *Biochem. biophys. Res. Commun.* 74, 714–719 (1977).
98. Painter, R. B., Clarkson, J. M. & Young, B. R. *Radiat. Res.* 56, 560–564 (1973).
99. Clarkson, J. M. & Painter, R. B. *Mutat. Res.* 23, 107–112 (1974).
100. Hart, R. W. & Setlow, R. B. *Mech. Ageing Devel.* 5, 67–77 (1976).

Mr. Scheuer. Thank you very much, Dr. Setlow.

Dr. Roger O. McClellan from the Lovelace Inhalation Research Institute.

STATEMENT OF ROGER O. McCLELLAN, PRESIDENT, LOVELACE INHALATION TOXICOLOGY RESEARCH INSTITUTE, ALBUQUERQUE, N. MEX.

Dr. McClellan. Thank you. Good afternoon Mr. Chairman and members of the subcommittee.

I am Roger O. McClellan, I am a toxicologist and research manager whose primary interests are in the conduct of research that will provide an improved basis for estimating the potential health impacts demand from environmental or occupational exposure to various pollutants. Currently, I serve as president and director of the Lovelace Inhalation Toxicology Research Institute in Albuquerque, N. Mex.

By way of background, this institute is one of the specialized laboratories which is Government-owned and equipped. It's operated under a cost-reimbursable, no-fee contract for the Department of Energy by the Lovelace organization. The program of this institute is appropriated for a specialized Department of Energy laboratory focusing on the problem of toxicity of airborne materials, especially those potentially released from energy generating or use activities.

An appropriate starting point today in considering the Department of Energy's health and environmental research budget is provided by a quotation from the budget address last year of the President. He said:

> Our goal was and remains economic recovery, the return of non-inflationary and sustained prosperity. We seek a larger economic pie to provide all Americans more jobs, more after-tax income, and a better life.

Stated succinctly, we desire a stronger economy and a better life. In my opinion, both of these are influenced to a large degree by the research that is carried out in the program under consideration today.

On the one hand, there is wide agreement that a stronger economy must be based on new technology, capital investment, and the availability of energy. A steady supply of energy in future is best assured by utilizing a diverse range of energy technologies.

On the other hand, a better life obviously includes provision of an environment that does not pose unreasonable risks to my health or that of my fellow man or woman, at home, at work, or at play. Good health includes not only freedom from overt disease, but a pleasant environment.

Thus, I think society is asking for the benefits of using energy and technology while at the same time asking that they not result in unreasonable health and environmental risks. To me, this goes to the heart of the Department of Energy's health and environmental research program—aiding in provision of an uninterrupted supply of energy without unacceptable health and environmental risks.

How is this goal to be achieved? In my view, it is to be achieved by obtaining a broad base of knowledge and then using that knowledge wisely to make decisions concerning the development and use of various energy options. Both are essential—knowledge and wise decisionmaking.

I am concerned that the administration's proposed budget for health and environmental research will not allow us as a nation to develop the base of information needed for making wise decisions in the future. The two principal programs concerned with the health and environmental impacts of energy, those of DOE and EPA, have been sharply reduced since 1982. The EPA's program has all been but eliminated. The DOE's program is only a few steps away from its potential demise. I am concerned that the efforts to reduce these budgets in part although striving to achieve laudatory objectives in terms of reducing regulations, they go about it inappropriately.

In the absence of knowledge, we will have ignorance. Decisions to regulate or not regulate or to promote or not promote a given energy option made in ignorance by administrative fiat have a high probability of not standing the test of time. Reversal at a later time for environmental, or economic reasons, or because of growing uncertainity will be expensive. One need only consider debates over acid rain, formaldehyde carcinogenicity, plutonium carcinogenicity, the health effects of diesel exhaust, or the results of human inhalation exposure to asbestos or radon and radon daughters, to appreciate how inadequate knowledge can create chaos and economic hardship or in the latter two cases, serious human health consequences.

I am not suggesting that I or others have a perfect vision of the future and potential environmental issues that must be addressed now to avoid future problems. However, I do think that collectively we have sufficient vision that we can carry out a highly cost-effective research program.

Let me illustrate the nature of the program with two examples; the question of the health effects of diesel exhaust and plutonium.

In 1977, the automotive industry was making plans to increase their production of diesel-powered vehicles. In that year, the Environmental Protection Agency, using the Ames bacterial mutagenicity assay, an assay that was developed in part with funding from predecessor organizations at the Department of Energy, demonstrated that organic extracts of diesel exhaust soot particles were very effective mutagens; very effective in altering the genetic material in cells Dr. Setlow has discussed with you.

This raised concern over the potential for the health effects of diesel exhaust potential for producing lung cancer and triggered a polarized argument. The automotive industry was on one side and EPA on the other; a classic confrontation between the promoter and the regulator.

At that stage our institute was asked by the Department of Energy to undertake a research program that would assist in resolving the uncertainty. The program we initiated was not a traditional toxicity-testing program designed to give a yes or no regulatory-oriented answer. It was a research program within the traditions of the Department of Energy's program directed at understanding the nature of the diesel exhaust, its movement to people, its deposition and fate in the body and, ultimately, the way in which disease was produced, if it was produced.

As a result of this research and complementary work done by the EPA, industry, and others, we have learned a great deal about diesel exhaust and its potential for producing ill health. The research has been multifaceted extending from pure chemicals to complex mixtures and from test tube systems, if you will, with cells and tissues to animals exposed to varying levels of diesel exhaust. As a result of this approach, we have begun to understand how the positive results of the original mutagenicity assays in bacteria can be reconciled with our failure to date to demonstrate lung cancer induction in animals and people.

All of the answers are not in but I think we can say with confidence that it is not likely that the use of diesel vehicles will cause an epidemic of cancer. This is reassuring; it has an obvious impact on how we continue to use diesel vehicles, diesel engines in trains, trucks, and cars.

Beyond answering specific questions about diesel-exhaust emissions, the research has provided new knowledge that has broader application to evaluating other energy technologies that involve complex mixtures of organic compounds and have potential for producing lung cancer. This work on complex mixtures is also a good example of how the DOE program complements research sponsored by other agencies such as the national taxicology program within the National Institutes of Health, which focuses primarily on specific compounds.

Let me turn next to the question of plutonium toxicity. Large quantities of plutonium are produced and used in our national defense program and in the nuclear-power industry. It has been deemed essential to conduct research to understand the potential health effects of plutonium. This again has included studies with different forms of the material in cellular and tissue systems, in whole animals and in people.

Early results on the toxicity of plutonium emphasize the need for handling it with extreme caution. As a result only a relatively few people have been accidently exposed to levels which result in body burdens of plutonium that are readily detected. These people, however, have been intensively studies, and no ill effects attributable to plutonium have been detected. In the absence of any positive data in people, the parallel studies with cells, tissues, and animals have been especially important. These studies have allowed us to define what diseases might be produced in man: specifically focusing our concern on cancer of the lung, liver, and skeleton. Moreover, the laboratory studies have given insight into the mechanisms by which plutonium produces cancer and methods which may be used to treat accidentally exposed individuals.

As in the case of the research on diesel exhaust, all of the answers are not in at the present time, however, the results provide a basis for estimating the likely impact of plutonium exposures and the degree of control needed to minimize human exposures and disease. These findings have played a critical role in how our national defense program has been conducted and in our use of nuclear reactors for power

In short, for these two illustrations, the picture is better defined today because carefully planned research was conducted to acquire new and relevant knowledge. Both of the examples that I have given address the potential impacts of technology in the health of people. They are typical of the issues being addressed in the Department of Energy's health and environmental research program.

I am convinced that support for research in this area is the responsibility of the Federal Government. It will not be adequately supported from other sources.

During the past 5 years, much has been learned that allows us to scope the potential health impacts of a wide range of energy technologies. The Department has supported research focused on specific technology such as coal gasification, liquefaction, solar applications, conservation measures, and the use of alternative fuel. Much of this work has involved close collaboration between biomedical and environmental scientists, on the one hand, and engineer and physical scientists developing the technologies. The body of information that has been developed is impressive. On close examination it is apparent that there are important generic issues that extend across several of the technologies that must now be addressed if we are to have an adequate understanding of how complex mixtures of chemicals associated with energy technologies that are used now or will be used in the future can affect man's health.

We are now in an advantageous position to conduct research that is oriented to the future. Using what has been learned, the scientists funded by the Department of Energy have planned research programs that with adequate support will provide us with the knowledge needed in the future to make wise decisions as to how best meet our energy needs without incurring unreasonable health risks. These are well-reasoned plans; they do not represent a crash program of willy-nilly spending; they are plans that should be carried out not to take advantage of the momentary absence of an energy crisis.

Unfortunately, the ability to carry out the needed research will be severely crippled if the administration's fiscal year 1980 budget is enacted. The severe budget reductions of fiscal year 1983 have already sharply curtailed energy-related health effects research in this country. The budget proposed for fiscal year 1984 will take a further toll.

The budget cuts translate into the loss of hundreds of scientists and supporting personnel from a national program to understand the health impacts of energy technologies on man and the environment. These are dedicated individuals that are members of research teams—teams that have taken years to develop. They represent the intellectual capital that will be sorely missed in 5 to 10 years and difficult to replace if the teams are dismantled today.

To me, the message is clear. We need to replace the approach all too frequently taken in the past of offering to society one unrealized solution after another with a well-reasoned long-range plan. We as a nation need to decide how much health and environmental research we are going to support to achieve this objective and then get on with the job by providing a degree of stability and consistent direction that has not been present over the last decade.

Thank you, Mr. Chairman.

[The prepared statement of Dr. McClellan follows:]

STATEMENT OF
DR. ROGER O. McCLELLAN
BEFORE THE
SUBCOMMITTEE ON NATURAL RESOURCES, AGRICULTURE RESEARCH AND ENVIRONMENT
OF THE
COMMITTEE ON SCIENCE AND TECHNOLOGY
U. S. HOUSE OF REPRESENTATIVES
March 3, 1983

Good afternoon, Mr. Chairman and members of the subcommittee.

I am Roger O. McClellan. I am a toxicologist and research manager whose primary interests are in the conduct of research that will provide an improved basis for estimating the potential health impacts to man from environmental or occupational exposure to various pollutants. For over 20 years, I have studied the effects of internally-deposited radionuclides with special reference to the nuclear power industry. During the past 10 years, my interests have broadened to include concern for a wide range of materials released from different energy technologies. Currently, I serve as President and Director of the Lovelace Inhalation Toxicology Research Institute in Albuquerque, New Mexico. A more detailed personal resume is attached as Appendix A.

By way of background, the Institute is a specialized government-owned and equipped laboratory operated under a cost-reimbursable, no-fee contract for the United States Department of Energy by the Lovelace Biomedical and Environmental Research Institute, a non-profit corporation. The Institute's staff, 75 professional and 150 supporting personnel, conduct an extensive research program focusing on the toxicity of airborne materials, especially those potentially released from energy generating or use activities. The program is a balance of basic and applied and short- and long-term research.

I am appearing today at your request to discuss the Department of Energy's Health and Environmental Research program. The following remarks, which reflect my own personal opinion, are based on:

1. My experience as a scientist and research manager;
2. My knowledge of the research being conducted by many of the national laboratories, specialized government laboratories, private industry and universities;
3. My service on a number of advisory groups of government agencies and the National Academy of Sciences; and
4. A detailed review of the budget for the Department of Energy's Office of Health and Environmental Research, the "Budget of the United States Government - Fiscal Year 1984" and supporting budget documents.

An appropriate starting point for considering the Department of Energy's Health and Environmental Research budget is provided by a quote from the President's budget message of February 8, 1982 –

> "Our goal was and remains economic recovery - the return of non-inflationary and sustained prosperity. We seek a larger economic pie to provide all Americans more jobs, more after-tax income, and a better life."

Stated succinctly, we desire a stronger economy and a better life. In my opinion, both of these are influenced to a large degree by the research carried out in the program under consideration today.

On the one hand, there is wide agreement that a stronger economy must be based on new technology, capital investment and the availability of energy. A steady supply of energy in the future is best assured by utilizing a diverse range of energy technologies.

On the other hand, a "better life" obviously includes provision of an environment that does not pose unreasonable risks to my health or that of my fellow man at home, at work or at play. Further, good health for me includes not only freedom from overt disease, but a pleasant environment that I enjoy seeing, smelling, tasting and touching.

Thus, society is asking for the benefits of using energy and technology while at the same time asking that their use not result in unreasonable health and environmental risks. To me, this goes to the heart of the Department of Energy's Health and Environmental Research program - aiding in provision of an uninterrupted supply of energy without unacceptable health and environmental risks.

How is this goal to be achieved? In my view, it is to be achieved by obtaining a broad base of knowledge and then using that knowledge wisely to make decisions concerning the development and use of various energy options. Both are essential - knowledge and wise decision making.

I am concerned that the Administration's proposed budget for health and environmental research will not allow us as a nation to develop the base of information needed for making wise decisions in the future. The two principal programs concerned with the health and environmental impacts of energy, those of the Department of Energy and the Environmental Protection Agency have been sharply reduced from 1982. The Environmental Protection Agency's energy program has all but been eliminated. The Department of Energy's program is only a few steps away from its potential demise. I am concerned that these reductions, in part, relate to a desire "to shackle the regulatory juggernaut that burdened production, consumed jobs and diminished productivity."

In the absence of knowledge, we have ignorance. Decisions to regulate or not regulate or to promote or not promote a given energy option made in ignorance by administrative fiat have a high probability of not standing the test of time. Reversal at a later time for environmental or economic reasons or because of growing uncertainty will be expensive. One need only consider debates over acid rain, formaldehyde carcinogenicity, plutonium carcinogenicity, the health effects of diesel exhaust or the results of human inhalation exposures to asbestos or radon and radon daughters (uranium mining) to appreciate how inadequate knowledge can create chaos and economic hardship or in the latter two cases, serious human health consequences.

I am not suggesting that I or others have a perfect vision of the future and the potential environmental issues that must be addressed now to avoid future problems. However, I do think that collectively we have sufficient vision that we can carry out a highly cost-effective research program. I have outlined in Attachment B my views on the nature of the Department of Energy's health-related research program.

Let me illustrate the nature of that program with two examples; the question of the health effects of diesel exhaust and plutonium.

In 1977, the automotive industry was making plans to increase their production of diesel-powered vehicles substantially. In that year, the Environmental Protection

Agency, using the Ames bacterial mutagenicity assay,[1] demonstrated that organic extracts of diesel exhaust soot particles were effective mutagens. This raised concern over the potential for inhaled diesel exhaust inducing lung cancer and triggered a polarized argument. The automotive industry was on one side and the Environmental Protection Agency on the other; a classic confrontation between the promoter and the regulator.

At the height of uncertainty over the health effects of diesel exhaust, our Institute, in 1979. was asked by the Department of Energy to undertake a research program that would assist in resolving the uncertainty. The program we initiated was not a traditional toxicity testing program designed to give a yes or no regulatory-oriented answer. It was a research program[2] directed at understanding (a) the physical and chemical nature of diesel exhaust, (b) its movement to the breathing zone of people, (c) its deposition and fate in the body when inhaled and, ultimately, (d) the way in which disease was produced, if it was produced.

As a result of this research and complentary work done by the Environmental Protection Agency, industry and others, we have learned a great deal about diesel exhaust and its potential for producing ill health. The research has been multifaceted extending from work with pure chemicals to complex mixtures and from test tube systems with cells and tissues to animals exposed to varying levels of diesel exhaust. As result of this integrated, multidisciplinary approach, we have begun to better understand how the positive results of the original mutagenicity assays of diesel exhaust extracts in bacteria can be reconciled with our failure to date to demonstrate lung cancer induction in animals and people exposed to diesel exhaust.

All of the answers are not in at the present time but we can say with some confidence that it is not likely that use of diesel vehicles will cause an epidemic of cancer. This is reassuring; it has an obvious impact on whether we continue to use diesel engines in trains, trucks and cars; the decision to regulate or not regulate diesel emissions and if regulated, how they will be regulated.

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[1] The Ames bacterial mutagenicity assay was developed by Dr. Bruce Ames and associates at the University of California-Berkeley with support from the U. S. Department of Energy and its predecessor organizations.

[2] The research program developed to evaluate the potential health effects of diesel exhaust is typical of the broad orientation of much of the Department of Energy's Health and Environmental Research program. Some summary "comments on Direction of Energy-Related Health Research" are attached as Appendix B.

The research results have clear implications for our national economy as impacted by the "health" of the transportation sector and our national needs for petroleum.

Beyond providing specific information on diesel exhaust emissions, the research has provided new knowledge that has broader application. For example, the work with diesel exhaust particles provides insight into how the body handles complex mixtures of organic compounds when they are associated with particles. Results have indicated that the retention half-time of some organic compounds in the lung is increased when they are inhaled as part of a complex mixture. This type of information must be considered when evaluating other energy technologies that involve complex mixtures of organic compounds and estimating their potential for producing lung cancer. This work on complex mixtures is also a good example of how the DOE program complements research sponsored by the National Toxicology Program which focuses primarily on specific compounds.

Let me turn next to the question of plutonium toxicity. Large quantities of plutonium are produced and used in our national defense program and in the nuclear power industry. It has been deemed essential to conduct research to understand the potential health effects of plutonium. This has included studies with different forms of plutonium in cellular and tissue systems, in whole animals and in people.

Early results on the toxicity of plutonium emphasize the need for handling it with extreme caution. As a result, only a relatively few people have been accidently exposed to levels which result in body burdens of plutonium that are readily detected. These people, however, have been intensively studied and no ill effects attributable to plutonium have been detected. In the absence of any positive data in people, the parallel studies with cells, tissues and animals have been especially important. These studies have allowed us to define what diseases might be produced in man: concern that focuses principally on cancer of the lung, liver and skeleton. Moreover, the laboratory studies have given insight into the mechanisms by which plutonium produces cancer and methods which may be used to treat accidently exposed individuals.

The research with plutonium has also contributed substantially to our general understanding of how the body handles inhaled particles. The results illustrate the importance of particle size in determining the rate at which particles are solubilized and also cleared from the respiratory tract by mucociliary action.

Further, the finding of cancers of the skeleton following inhalation of plutonium emphasizes the importance of considering diseases in organs other than the lung for inhaled material.

As in the case of the research on diesel exhaust, all of the answers are not in at the present time, however, the results provide a basis for estimating the likely impact of plutonium exposures and the degree of control needed to minimize human exposures and disease. These findings have played a critical role in how our national defense program has been conducted and in our use of nuclear reactors for power.

In short, for diesel exhaust emissions and plutonium, the picture is better defined today because carefully planned research was conducted to acquire new and relevant knowledge. With both materials, there are still unresolved questions; What are the effects of very low levels of exposure? Does exposure to plutonium or diesel exhaust at low levels potentiate the effects of the leading cause of lung cancer - smoking? Do other life style or occupational factors influence the likelihood of disease from diesel exhaust or plutonium?

I am confident the questions that I have posed above as well as others can be answered with a well-planned and adequately supported research program. Because of the complexity of these questions, there is need to use a team approach that draws on the talents of a number of scientific disciplines. As in the past, it is necessary to utilize a range of approaches including studies with macromolecules, cells and tissues, whole animals and people. Because the primary disease of interest is cancer, which generally occurs late in life, it will be necessary to conduct at least some very long-term studies.

Both of the examples address the potential impacts of technology on the health of people. They are typical of the issues being addressed in the Department of Energy's Health and Environmental Research program. I am convinced that support for research in this area is the responsibility of the federal government. It will not be adequately supported from other sources.

During the past five years, much has been learned that allows us to scope the potential health impacts of various energy technologies. The Department has supported research focused on specific technologies such as coal gasification and liquefaction, solar applications, conservation measures and the use of alternative fuel while continuing at a reduced level of research related to the use of nuclear power. Much of this work has involved close collaboration between biomedical and environmental scientists and the engineers and physical scientists developing the technologies. The body of information that has been developed is impressive. On first glance, much of the information appears descriptive and is technology or site specific. However, on closer examination, it is apparent that there are important generic issues that extend across several technologies that must be addressed if we are to have an adequate understanding of how complex mixtures of chemicals associated with energy technologies that are used now or will be used in the future can affect man's health. For details of many of these issues, I urge you to consider the recent National Academy of Science "Report of the Research Briefing Panel on Human Health Effects of Hazardous Chemical Exposures."

We are now in an advantageous position to conduct research that is oriented to the future. Using what has been learned, the scientists funded by the Department of Energy have planned research programs that with adequate support, will provide us with the knowledge needed in the future to make wise decisions as to how to best meet our energy needs without incurring unreasonable health risks. These are well-reasoned plans; they do not represent a crash program of "willy-nilly" spending; they are plans that should be carried out now to take advantage of the momentary absence of an energy crisis.

Unfortunately, the ability to carry out the needed research will be severely crippled if the Administration's FY-1984 budget is enacted. The severe budget reductions of FY-1983 have already sharply curtailed energy-related health effects research in this country. The budget proposed for FY-1984 will take a further toll.

These budget cuts translate into the loss of hundreds of scientists and supporting personnel from a national program to understand the health impacts of energy technologies on man and the environment. I can assure you that the people whose services must be terminated are not paper shuffling bureaucrats writing regulations or scientists doing meaningless experiments; they are dedicated individuals that are members of research teams that have taken years to develop. They represent intellectual capital that will be sorely missed in five to ten years and difficult to replace if the teams are dismantled today.

To me, the message is clear. We need to replace the approach all too frequently taken in the past of offering to society one unrealized solution after another (i.e., Burn more coal! Nuclear power is the way! Solar will save us! High technology is the answer!) with a well-reasoned long-range plan. To me it is obvious we are not going back to the dark ages. Technology is here to stay, but the use of any technology requires an understanding of its potential health and environmental impacts. The public wants jobs, but it does not want unacceptable health and environmental risks. We, as a nation, need to decide how much health and environmental research we are going to support to achieve this objective and then get on with the job by providing a degree of stability and consistent direction that has not been present over the last decade.

APPENDIX A

CURRICULUM VITAE

ROGER O. McCLELLAN

President/Director, Inhalation Toxicology Research Institute, Lovelace Biomedical and Environmental Research Institute

Business Address	Home Address
P. O. Box 5890 Albuquerque, NM 87185	1111 Cuatro Cerros S.E. Albuquerque, NM 87123
(505) 844-6835	(505) 296-7083

Date of Birth:	January 5, 1937
Place of Birth:	Tracy, Minnesota
Married:	June 23, 1962 to the former Kathleen Mary Dunagan
Children:	Eric John 7-17-65; Elizabeth Christine 7-24-67; Katherine Ruth 4-9-70
Social Security #:	539-32-6724

EDUCATION:

Doctor of Veterinary Medicine with Highest Honors. Washington State University Pullman, Washington, 1960
Master of Management, Robert O. Anderson Graduate School of Management, University of New Mexico, Albuquerque, NM, 1980

PROFESSIONAL LICENSURE AND CERTIFICATION (by examination):

Veterinary Medicine, State of Washington, 1960
American Board of Veterinary Toxicology, Diplomate, 1967
American Board of Toxicology, Certificate, General Toxicology, 1980

EXPERIENCE:

1976 - present	President and Director, Inhalation Toxicology Research Institute, Lovelace Biomedical and Environmental Research Institute, Albuquerque, New Mexico
1973 - 1976	Vice President and Director of Research Administration and Director, Inhalation Toxicology Research Institute, Lovelace Foundation for Medical Education and Research, Albuquerque, New Mexico
1966 - 1973	Assistant Director of Research and Director, Fission Product Inhalation Program, Lovelace Foundation for Medical Education and Research, Albuquerque, New Mexico
1965 - 1966	Scientist, Medical Research Branch, Division of Biology and Medicine, U. S. Atomic Energy Commission, Washington, D.C.
1965	Senior Scientist, Biology Department, Pacific Northwest Laboratories, Battelle Memorial Institute, Richland, Washington (leave of absence to the U. S. Atomic Energy Commission)
1963 - 1964	Senior Scientist, Biology Laboratory, Hanford Laboratories, General Electric Company, Richland, Washington
1959 - 1962	Biological Scientist, Biology Laboratory, Hanford Laboratories, General Electric Company, Richland, Washington

EXPERIENCE Cont'd.:

1957 - 1958	(Summers) - Junior Scientist, Biology Laboratory, Hanford Laboratories, General Electric Company, Richland, Washington
1957 - 1960	Research Assistant, Department of Veterinary Microbiology, Washington State University, Pullman, Washington

ACADEMIC AFFILIATIONS:

1970 - present	Adjunct Professor, Department of Radiation Sciences, School of Pharmacy, University of Arkansas Medical School, Little Rock, AR
1971 - present	Clinical Associate, Department of Pathology, The University of New Mexico School of Medicine, Albuquerque, New Mexico
1973 - 1981	Adjunct Professor, Department of Biology, The University of New Mexico, Albuquerque, New Mexico
1980 - present	Adjunct Professor, Department of Veterinary and Comparative Anatomy, Pharmacology and Physiology and member, Graduate Faculty of the Program in Veterinary Science, College of Veterinary Medicine, Washington State University

APPOINTMENTS

1967 - 1973	Member — Joint Space Nuclear Systems/Biomedical and Environmental Research Working Group
1968 - 1970	Advisor — Laboratory Animal Biology and Medicine Training Program, University of California-Davis
1968 - 1971	Consultant — National Institute of Environmental Health Sciences, National Institutes of Health
1969 - 1973	Member — Toxicology Study Section, National Institutes of Health
1970 - 1975	Member — Subcommittee on Whole Animal Radiobiology & Pathology - Los Alamos Meson Physics Facility (LAMPF)
1973 - 1976	Member — Advisory Board on Veterinary Specialties, AVMA
1975 - 1976	Member — Biomedical Advisory Committee on Health Effects for Reactor Safety Study to the Nuclear Regulatory Commission
1971 - present	Member — National Council on Radiation Protection and Measurements (Program Committee, Member, 1977-1981, Chairman, 1981)
1969 - 1979	Chairman — Scientific Committee #30 of National Council on Radiation Protection and Measurements
1977 - present	Member — Scientific Committee #57 of National Council on Radiation Protection and Measurements
1976 - 1977	Member — *Ad Hoc* Committee on 'Internal Emitters', National Council on Radiation Protection and Measurements
1972 - 1980	Member — Transuranium Technical Group (Advisory to U. S. Department of Energy)
1972 - 1977	Member — Environmental Radiation Exposure Advisory Committee of the U. S. Environmental Protection Agency (Chairman 1974 - 1977)
1974 - 1980 1981 - present	Member — Executive Committee, Science Advisory Board, U. S. Environmental Protection Agency

APPOINTMENTS Cont'd.:

1977 - 1978	Chairman — Ad Hoc Review Committee on Scientific Criteria for Environmental Lead, Science Advisory Board, U. S. Environmental Protection Agency
1978 - 1980	Chairman — Ad Hoc Review Committee on U. S. Environmental Protection Agency 5-Year Research Plan, Science Advisory Board
1978 - 1979	Co-Chairman — Ad Hoc Committee on U. S. Environmental Protection Agency Health Effects Research Program
1974 - 1978	Member — National Institutes of Health, Animal Resources Advisory Committee
1974 - present	Member — North American Late Effects Group Steering Committee
1976 - 1980	Associate Editor — Laboratory Animal Science
1974 - 1976	Member — Ad Hoc Committee - "Hot Particles" - Advisory Committee on the Biological Effects of Ionizing Radiations (BEIR) — National Research Council/National Academy of Science
1977 - 1980	Member — Committee on Animal Models for Research on Aging, Institute of Laboratory Animal Resources, National Research Council/National Academy of Science
1977 - 1980	Chairman — Subcommittee on Carnivores, Committee on Animal Models for Research on Aging, Institute of Laboratory Animal Resources, National Research Council/National Academy of Science
1977 - 1980	Member — Enewetak Atoll Cleanup Advisory Group (Advisory to U.S. Department of Energy)
1978	Chairman — Health Effects Panel, Environmental Impact of Oil Shale Technology Workshop (EPA, DOE, HEW sponsored)
1979 - present	Member — National Academy of Science/National Research Council, Committee on Toxicology, Chairman, 1980 - present
1980 - present	Ad Hoc Member — Board on Toxicology and Environmental Health Hazards, National Research Council/National Academy of Science
1980 - present	Member — Environmental Health Committee, Science Advisory Board, U. S. Environmental Protection Agency (Chairman, 1982 - present)
1980 - present	Member — Ad Hoc Clean Air Scientific Advisory Committee on Health Effects of Sulfur Oxide and Particulate Matter, U. S. Environmental Protection Agency
1980 - present	Member — Editorial Board, Journal of Toxicology and Environmental Health
1980 - present	Member — DOE Dose Assessment Advisory Group
1981 - present	Member — Health Research Committee, The Health Effects Institute
1982 - present	Board of Directors, Toxicology Laboratory Accreditation Board

PROFESSIONAL AFFILIATIONS AND HONORARIES:

Health Physics Society (Program Committee 1970-1973 and Chairman - 1972)
Elda E. Anderson Award - Health Physics Society (1974)
Radiation Research Society (Secretary/Treasurer - 1982 - present)
American Association for the Advancement of Science (Fellow)
American Board of Veterinary Toxicology (Diplomate 1967; President 1970-1973)
American Board of Toxicology (Certification - General Toxicology, 1980)
American College of Veterinary Toxicologists (Councilman 1968-1971)
American Veterinary Medical Association
American Association for Aerosol Research (Board of Directors, 1982 -)
New Mexico Veterinary Medical Association
New Mexico Zoological Society (Board of Directors - 1970-1972)
Washington State Veterinary Medical Association
Society for Experimental Biology and Medicine
Society for Risk Analysis
Society of Toxicology (Committee on Legislative Assistance, 1978-1980; Program Committee, 1980-1983; Committee on Professional Relations and Standards, 1982-1983)
Sigma Xi
Phi Kappa Phi
Phi Zeta
Alpha Psi

GUEST LECTURER:

University of Washington
Washington State University
University of California-Davis
Ohio State University
University of New Mexico
University of Kansas
West Virginia University

AREAS OF INTEREST

Dr. Roger O. McClellan's research interests are centered in two broad areas; (1) inhalation toxicology, and (2) late effects of internally-deposited radionuclides. He is particularly interested in the conduct of animal experimentation to develop information that may be used to predict the consequences of accidental exposure of man or establish standards to assure the safe and orderly conduct of activities that may result in release of toxic agents to man's environment. His recent research has been concerned with airborne materials associated with a wide range of energy technologies including nuclear power, coal combustion and gasification, and use of diesel-powered vehicles. In each area, his research has spanned from the conduct of animal toxicity studies to the development of quantitative assessments of the risk to man.

In addition to his direct research interests, Dr. McClellan has had a continuing interest in organizational management, especially the management of research. His activity in this area has centered on the management of a multidisciplinary team of professionals, technicians and support personnel to address complex problems including the use of a matrix management approach.

PUBLICATIONS AND PRESENTATIONS

Dr. McClellan is author or co-author of over 200 scientific publications, abstracts and document reports and has given numerous presentations before scientific and lay audiences.

March 3, 1983

APPENDIX B

COMMENTS ON DIRECTION OF ENERGY-RELATED HEALTH RESEARCH

Roger O. McClellan, D.V.M.
Lovelace Inhalation Toxicology Research Institute
P. O. Box 5890, Albuquerque, NM 87185

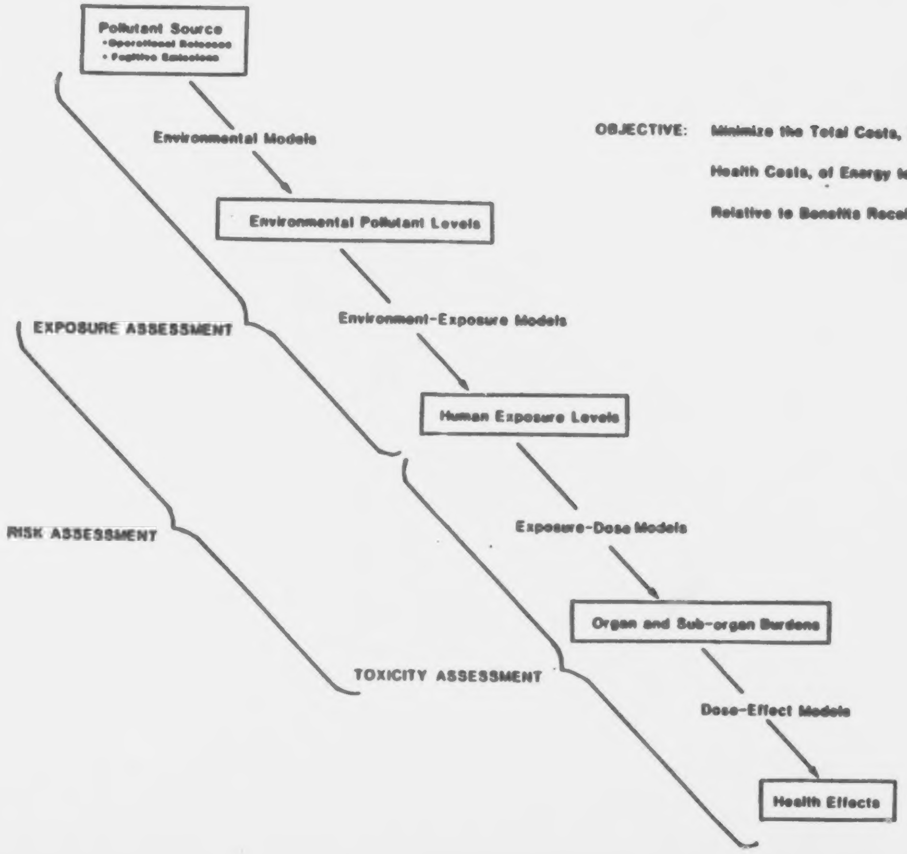
In my view, the overall objective of the health-related research of the Department of Energy (DOE) is to provide an information base that will allow development and deployment of energy technologies in a manner that will minimize health costs relative to the overall benefits received by society. This requires the conduct of research that is based on substantial knowledge of current and developing energy technologies so that it can have a high degree of relevance. The program specifically focuses on health issues related to energy and complements health research supported by other agencies. The DOE is the only agency that is concerned with the impacts of the total energy cycle. It goes without saying thst the research must be of high quality and conducted with scientific independence so that information obtained will be viewed with confidence by other scientists, other parts of DOE and society at large.

The energy technology orientation ranges from consideration of those now in use (e.g., coal combustion and nuclear power), to those with near to intermediate term application (e.g., coal gasification and liquefaction, oil shale) to those that may be important in the next century (e.g., fusion). This includes consideration of all energy producing, consuming and conserving activities. This, of necessity, includes such diverse activities as mining and retorting of oil shale, production and use of photo-voltaic devices, distribution and use of synthetic fuels, disposal of wastes and use of man-made insulating materials. The research addresses exposures of both workers and the general public.

I favor a research program that is strongly oriented to providing information that will allow assessment of health risks in people as illustrated in the attached figure. This orientation recognizes the importance of developing knowledge of pollutant sources and environmental levels resulting from operational, fugitive and accidental releases. It requires characterization of these materials in the workplace, indoor and general environment with special reference to how they reach man and the form in which this occurs. In this area, special care must be taken

INTEGRATED APPROACH TO EVALUATING HEALTH RISKS OF ENERGY TECHNOLOGIES

OBJECTIVE: Minimize the Total Costs, Including Health Costs, of Energy to Society Relative to Benefits Received


Pollutant Source
• Operational Releases
• Fugitive Emissions
Environmental Models
Environmental Pollutant Levels
Environment-Exposure Models
Human Exposure Levels
Exposure-Dose Models
Organ and Sub-organ Burdens
Dose-Effect Models
Health Effects
EXPOSURE ASSESSMENT
TOXICITY ASSESSMENT
RISK ASSESSMENT

to separate the consequential from the non-consequential recognizing that everything that is measurable does not necessarily pose a health risk and that energy-related pollutants are only a part of the total environment.

The next logical area of concern is how pollutants enter and are distributed within the body following inhalation, ingestion or other forms of exposure. This area of research is oriented toward establishing an understanding of the relationship between exposure and the concentrations of materials that are available for interaction with critical organelles, cells and tissues and the pollutant, environment and host factors that influence this relationship.

The next area of research is directed toward understanding the cause-effect relationships between tissue concentrations of individual pollutants and mixtures and diseases in man. In considering which pollutants or mixtures to study, priority must be given to those encountered or likely to be encountered in high concentration by man and those with high likelihood of producing deleterious effects. The research addresses a wide range of health effects from those that are viewed as temporary physiological alterations to those that are irreversible and permanently impair an individual's physical or mental abilities and those that impact on future generations. Because most occupational and environmental exposures to energy-related pollutants are at low levels, the emphasis within the research program must be on late-occurring diseases such as cancer.

The research program seeks to take advantage of any human exposure situations that provide the opportunity to better understand the induction of diseases by energy pollutants. However, recognizing that such opportunities are fortunately limited, the majority of the health-related research must be conducted in other species and include studies at whole animal, organ, tissue and lower levels. The studies performed include observations in systems (such as bacterial mutagenicity assays) that serve as possible predictors of late-occurring effects to systems that seek to directly identify late-occurring effects. Of necessity, effort must be directed to validating the capability of short-term tests for predicting the induction of late-occurring effects in laboratory animals and man and for extrapolating from laboratory animals to man.

The nature of the materials studied spans from specific elements or compounds to complex mixtures of materials identical to or mimicking those encountered or likely to be by man. Materials obtained directly from representative energy processes must be studied whenever they are available. However, a balanced approach must be taken to avoid pre-occupation with samples that are uniquely related to a specific process or site unless they are worthy of attention in their own right.

Recognizing that pollutants arising from energy technologies are only a part of the environment faced by people, it is important to investigate the potential interactions with other factors in the environment that may contribute in producing disease. Likewise, it is important to evaluate the influence of host factors such as age, occupation, social habits as well as health and nutritional status.

It is important that the program include a balance of research directed toward (a) development of a basic understanding of how the body handles and responds to energy pollutants, (b) the development of improved techniques for studying pollutant behavior and effects, and (c) the conduct of both short- and long-term toxicity assays of energy pollutants.

I view formalized risk assessments as an important part of the total research program. Such assessments provide a logical framework for assembling, analyzing and interpreting all of the available information that is relevant to estimating the health impacts of any energy process or technology. The estimated risks represent an integration of the products of the research effort. Moreover, they fill a valuable role in identifying information gaps, and therefore, research needs.

In summary, the DOE needs a health and environmental research program that sharply focuses on developing information needed to assess the health and environmental impacts of conventional and new energy technologies. A balanced program that includes studies of man, laboratory animals and simpler systems is necessary recognizing that adequate information on man *per se* is not available. The complexity of the issues being addressed requires research to be conducted in several diverse areas. Provision must be made for information from the several areas to be integrated including a joining of environmental and health-related information. To meet the needs of the Department on a long-term basis, some of the research will, of necessity, focus on a single energy technology, some will be applicable to several technologies while others will be of a supporting nature.

I will be pleased to discuss with you in greater detail my views on specific aspects of the research program including my priorities for research needed to assess the health impacts of energy technologies.

Mr. SCHEUER. Thank you very much, Dr. McClellan for your splendid testimony.

Now, Dr. Harvey Herschman of UCLA.

STATEMENT OF HARVEY R. HERSCHMAN, PH.D., PROFESSOR OF BIOLOGICAL CHEMISTRY, UCLA SCHOOL OF MEDICINE

Dr. HERSCHMAN. Thank you. In addition to that apparently indecipherable title that I had before, I am also the associate director of the laboratory of biomedical and environmental sciences. That's a so-called dedicated DOE laboratory that is integrated into the UCLA academic and research community. The lab was founded in 1947 by the Atomic Energy Commission and initially was set up with two objectives. First to deal with the impact of the irradiation on the environment, and second to develop the use of radioisotopes in biology and medicine just after the war. With the advent of the Department of Energy, the mission of the lab has broadened to some degree to include the investigation of the effects of energy-related processes and products on man and his environment.

Each principal investigator within our lab holds a position on the faculty at UCLA. My own program, the one that I have administrative responsibility for, has seven principal investigators. The UCLA biomedical and life sciences community has approximately 600 faculty members. As a consequence our integrated DOE lab of seven groups participates in, and has direct access to a related research community of extensive proportions. As a consequence, we don't have to provide, on a continuing basis with DOE funding, many of the technologically oriented facilities, such as structural labs or physical separations laboratories. We also have access to a number of physical resources such as libraries and computer facilities that are funded through other mechanisms that are open to the entire university-based scientific community, of which we are a part. We also collaborate with academic colleagues that have related interests on research programs that are of mutual interest. I bring this up because I would estimate that, in my own personal research project, about 30 to 50 percent of it is carried out in collaboration with UCLA faculty who are not members of the DOE laboratory or supported by them.

Probably the most important contribution that our interdigitation into the UCLA community makes is our access to this pool of Ph.D. graduate students and postdoctoral scholars. Since all of our staff members also are members of UCLA's faculty, we are able to take advantage of a variety of university, State, private, and other Federal non-DOE funds to support these postdoctorals and graduate students in training in their research while they carry out doctoral and postdoctoral work that is really relevant to the DOE programs. The majority of the research programs within our own division are concerned with the molecular and cellular explanations of how cells divide and also how one cell expresses a property that makes it different from another cell within the body. We have tried whenever possible—while still being concerned with the basic aspects of this science—to use as research tools the experimental systems that can address problems also of potential clinical significance.

Much of our work revolves around alterations in these basic cellular phenomena of cell division or expression of differentiated function as a consequence of exposure to environmental toxicants. Many of the studies focus on the uncontrolled growth that occurs as a consequence of carcinogenesis and also the consequent alterations that occur in cellular properties in response to these types of agents.

In the next few minutes what I will try to do is describe some examples of past and current research from our division. I'll probably talk about four or five examples.

In the first, it is well known that individuals who bear tumors suffer an extensive weight loss and, in fact, eventual starve as a result of the fact that their body fat is mobilized. The tumor recruits the normal deposits of body fat to become solubilized and the tumor then uses them for metabolism and synthesis. This, of course, occurs at the expense of the host, the person who bears the tumor. One of the research groups in our division has recently demonstrated that many tumors produce and secrete a factor which is able to induce this mobilization of stored body fat. The factor has been found in the blood of cancer patients; the primary attention of this research group now is directed toward purifying this factor, which is known as the lipid-mobilizing factor and characterizing its molecular structure. If we can elucidate how it works it should allow us to develop a means to counteract its action and this would help us to maintain the neutrational status of cancer patients.

Another example, when one burns fossil fuel you get the release of a large number of different types of chemicals. There's a group that is known as polyaromatic hydrocarbons—for time and simplicity I'm going to refer to these as PAH's. Many of these are very potent carcinogens. Their carcinogenicity, however, depends on the genetic makeup of the individual to which they are exposed. Various types of biochemical and genetic studies have shown that the reason for these individual differences in cancer that's induced by polyaromatic hydrocarbons is that the PAH itself is not actually the carcinogenic molecule. Instead, it is a product of the PAH, that's produced by an enzyme in the animal's tissues, that is the actual carcinogen. So, cells of the exposed animal have to convert the PAH to what is known as an ultimate carcinogen. It turns out that the level of this enzyme, this converting enzyme, is normally low, but after exposure to a PAH it is rapidly increased. This increase in this converting enzyme varies greatly from one individual to another. It turns out that individuals who are high in this inducible response for converting PAH's to the metabolite are in fact very susceptible to PAH-induced carcinogenesis because they have the converting enzyme. Those that are low in this inducible activity have a relatively reduced frequency of PAH cancer. All of this has been done with genetic strains of mice and a lot of recent evidence now suggests that this is true in individuals in the human population as well.

One of our research groups has developed a homogeneous population of cells that is altered in the various processes of this PAH recognition, another group in the enzyme induction and another group in metabolic conversion. Using these types of cells, I think we'll soon be able to work out the pathway of these converting enzymes as well as the mechanisms of the actual conversion of the precarcinogen to the actual carcinogen. By using recombinant DNA procedures the system is also being used to isolate the human gene that directs the synthesis of this particular enzyme. As a consequence of all this, I think we will soon understand the mechanism of this induction and by virtue of this approach, I hope, be able to screen for and identify individuals who are either unusually sensitive to or resistant to environmental PAH's.

I'd like to turn to another example. There is another group of compounds that one finds in the environment that are known as tumor promoters. These are agents that themselves are not really able to induce cancer. They don't promote cancer themselves. They can greatly potentiate the tumor-initiating potential of previous exposure to a carcinogen. If one first gets exposure to a low dose of a carcinogen, which is insufficient in itself to cause a tumor, if an individual subsequently comes in contact with one of these types of compounds, these tumor promoters, he may then subsequently develop a tumor. In experimental systems mice have been exposed to low doses of carcinogen, one which won't cause tumor formation and if a year later—in mouse time this mean a third of his lifetime later—he is exposed to a tumor promoter, he will subsequently develop a cancer within 6 to 10 weeks. These tumor promoters can call out the effect of a previous exposure to a subclinical dose of a carcinogen.

I believe that the development of methods for identifying tumor promoters and for understanding their modes of action are as important as identifying and understanding the actions of carcinogens. The identification of these agents has previously required a very time-consuming and expensive animal tests. In my own laboratory we have now developed a cell culture approach, which can indicate in only 3 days whether an agent is a member of one particular class of tumor promoters.

Mr. McGrath. Excuse me. That's very interesting to me. That sounds almost like an allergic reaction. You can tolerate so much to a point and then you become ill because of a recurrent intake of a certain compound.

Dr. Herschman. The exposure to a carcinogen need only be a single event. If the individual sees that and it's a low enough dose then there will be no clinical manifestation of that. Somehow that information is stored by the body because if he subsequently then sees one of these types of compounds, that I am referring to, then the tumor will be elicited. So there is some sort of memory and in that sense the allergic response does work, although by different biological mechanism. In a similar way you have a primary exposure to a compound which sensitizes you and subsequently down the line if you see it again you have a very violent response to it. In an allergic response case the initiating and promoting event are the same molecule. In this case the initiating event and the promoting event are different molecules. One needs a two-step mechanism in both of those sorts of biological phonemena to get deleterious action.

Ms. Schneider. I would like to ask a related question since we've already interrupted you.

If you have experienced one incident of exposure and there has been some chemical alteration within the body, but it has not yet, as you said, manifested itself in tumor form, are you as a researcher now today able to identify that molecular alteration that is existent, but yet has not manifested itself beyond the initial stage?

Dr. **Herschman**. We are not able to do that in the particular systems that we are working in. It is something we would like to be able to do. We would like to know whether we can recognize people who are at risk for all types of cancer. There is—not in my own laboratory—but very recent evidence that, for example, there is a gene which predisposes individuals to a particular type of cancer—bladder cancer—and in that particular system it is now possible, in fact, to recognize individuals that carry that gene.

You asked a very pertinent question because the experimental evidence for that came out last week.

Ms. **Schneider**. I've been very interested in this and studying it a bit, but I must admit I hadn't been reading the study that came out last week. Thank you.

Dr. **Herschman**. What we have done is devise a test which we think can recognize certain classes, at least, of these tumor promoters in a very brief period of time. One would then have to—we think this will provide a screen for these types of agents environment. One would have to verify them in the more expensive but more definitive animal tests.

A number of research groups in our lab also have applied immunological techniques to problems of tumor diagnosis and monitoring of patients that have tumors. I'll cite a couple of cases. The death rate from prostate cancer is in the United States is second only to lung cancer in men. My own laboratory, working in collaboration with the people at the Kaiser Hospital system in Los Angeles, developed a test for the presence in blood of a unique protein that is produced by the prostate gland. Patients who have prostate cancer have elevated circulating levels of this protein. This test is now commercially available and is used widely by physicians in the screening and the diagnosis and the monitoring of prostate cancer. I used to be able to cite the figures for how many lives and how many dollars we save with this test but, I must say I have not brought them with me.

We've also recently found, in collaboration with some colleagues in the departments of Surgery and Pathology at UCLA, that a protein we previously thought was found only in the nervous system turns out also to be present in over 95 percent of malignant melanomas that we have examined. It turns out that these tissues come from the same original type of tissue in the embryo and share this common marker. Using specific microscopic tests for this protein surgical pathologists can recognize small numbers of these metastatic melanoma cells in sites that are distant from the original tumor. The ability to distinguish the metastases of a melanoma from another type of cancer at a distant site can help the physician to determine the type of therapy that he subsequently will use.

Another group in our laboratory has been working with what is known as monoclonal antibody technology to define the presence of a new molecule on specific classes of brain tumors. The emphasis in that project now is to try and purify the antigen and to use a serologic test for screening for the presence of these types of tumors and for monitoring the level of the tumor burden and evaluating various types of therapy. In our lab we have had a lot of experience in coupling toxins to various types of molecules, either antibodies or growth factors, and the idea here is to produce what we call heterotoxins, mixtures of molecules that recognize a cell by virtue of a specific component of its surface and a toxic molecule. These are then able to preferentially kill target cells that carry specific surface antigens or hormone receptors or so on. We are now working on model studies to determine how efficiently these heterotoxins work in animals. Once we have optimized these types of studies we want to develop immunotoxins—portions of potent toxins chemically coupled to monoclonal antibodies directed against tumor-associated antigens—as another component of combined chemotherapy for specific types of cancer.

In the last minute or two, I would like to talk about this issue of optimizing productivity that we were asked to address. The research productivity is really the first and foremost on the presence of trained, creative scientists. Research programs aren't really single experiments. They are long-term programs that—whose goals and strategies last for periods of several years. As Roger pointed out, continuity is of great importance in these studies. The training, skill, and experience of a researcher who leaves one of these programs requires an enormous investment in terms of time, intellect, and finance to replace such an individual. Because our funding is on an annual basis. our individual programs have to be budgeted on an annual basis, and as a consequence we have to reconstruct or construct our individual budgets annually, often near the beginning of a fiscal year and frequently, as occurred this year, in the middle of a fiscal year. This, of course, make the programs less efficient since we can't plan very far in advance the complete staffing of our team. If it were possible to develop a budgeting program that defines units of research support for 3 to 5 years, I think, for the same amount of money we would get much greater productivity and we would require much less administration.

My own experience with these types of programs, when they are supported by charitable organizations such as the American Cancer Society, the American Heart Association, or other Federal agencies like the NIH or the NSH, certainly is consistent with what I am saying. I've found that I'm able to devote far more time to the scientific objectives and far less time to the administration.

Let me just use the final minute of this to comment on the impact of the 1984 budget. I hope I spent enough time telling you about examples of research to point out that there's not a direct correlation between dollars spent and research accomplishments. Nevertheless, any of our scientific hypotheses have to be verified, not simply by inspiration, but by experimentation. Biomedical research is skilled-labor intensive; it requires a lot of time at the laboratory bench.

Current projections for our particular institution included something like 25 percent reduction in the research support for our division. I don't want to cry wolf with you; our programs will continue, and I hope will achieve most, but certainly not all of our goals. We won't do them in the same time span. We have to still continue to do the type of experiments that result in either verification or refutation of our ideas. And it's necessarily going to take longer with fewer skilled associates to test these alternative hypotheses and carry out the verifying experiments that are necessary to move science forward in a believable and substantive fashion. The issue is one, that is to some degree qualitative, because it will eleminate people, but to a greater degree quantitative; my colleagues and I are committed to our scientific objectives in lifetime increments, not in fiscal years. I think that the rate at which we progress—which is an issue of great practical and social importance—is what is at issue here. Not our pursuit of our objectives. Thank you.

[The prepared statement of Dr. Herschman follows:]

Testimony of Harvey R. Herschman, Ph.D.

Professor of Biological Chemistry, UCLA School of Medicine;

I would like to begin by thanking Chairman Scheuer and the rest of the committee members for the opportunity to discuss our research programs. I hope to accomplish three objectives this morning. I will first describe the unique nature of the Division of Biomolecular and Cellular Sciences, a subdivision (for which I have administrative responsibility) of the Laboratory of Biomedical and Environmental Sciences. I will emphasize the advantages accruing from the integration of our DOE laboratory into the UCLA campus. Second, I will describe several of our research goals and examples of results from our laboratory. By so doing I hope to acquaint you with some current approaches in basic research in cellular processes, and highlight some of our recent studies that we hope will have an impact on cancer causation, detection and therapy. Finally, I will project the needs, as I see them, for optimal productivity for our program in the future, since I believe these views are likely to be generalizable to DOE programs with similar objectives.

The Laboratory of Biomedical and Environmental Sciences (LBES), a DOE-supported laboratory integrated into the UCLA academic and research program. The LBES was founded at UCLA in 1947 by the Atomic Energy Commission, and has been in continuous operation since that time. The Laboratory was originally set up to (1) deal with the impact of irradiation on the environment, and (2) to develop the use of radioisotopes in biology and medicine. With the advent of DOE the mission of LBES has broadened to include investigation of the effects of energy-related processes and products on man and his environment. LBES is headed by a Director, and has three research programs (the Division of Environmental Biology, the Division of Nuclear Medicine, and the Division of Biomolecular and Cellular Sciences), each headed by an Associate Director. There are 24 principal investigators in the LBES, each responsible for a major scientific program within one of these three subdivisions. Each principal investigator in the LBES holds a position on the faculty at UCLA; either in the College of Letters and Sciences, or in the School of Medicine. My own program, the Division of Biomolecular and Cellular Sciences, has seven principal investigators, each of whom has an academic appointment in the department of Biological Chemistry, Anatomy, Pathology or Medicine in the UCLA School of Medicine.

Our close physical, intellectual and academic proximity to UCLA provides the Laboratory and the DOE with a number of benefits. UCLA has approximately 600 faculty members in the biomedical and life sciences. This university is recognized as one of the outstanding graduate research facilities in the country, having recently been ranked in the top ten institutions in biochemistry and molecular biology. Colleagues with common research interests can be found in all of the life sciences and medical school departments (e.g. Biology, Microbiology, Immunology, Biological Chemistry, Chemistry, Anatomy, Pharmacology, Physiology, Pathology, Medicine, Surgery, etc.), and in organized research units of the University (e.g. the Brain Research Institute, the Jules Stein Eye Institute, the Molecular Biology Institute, the UCLA-Jonsson Comprehensive Cancer Center). Thus, our integrated DOE research unit of seven programs participates in, and has direct access to, a related research community of extensive proportions. We can (and do) take advantage, in a collaborative and collegial manner, of the extraordinary range of expertise, knowledge, and experience available at UCLA in the most specialized research activities. We therefore do not need to provide, on a continuing basis with DOE funding, many technologically oriented facilities (e.g. structural analysis, physical separations laboratories, culture fluid preparation). These are available -- through other funding mechanisms -- to the university-based scientific community, of which we are an integral component. Consequently, a remarkable physical resource of libraries, laboratory equipment and computational facilities are available to our staff. Moreover, we are able, when appropriate, to collaborate with academic colleagues with related interests on research programs of mutual interest. These facilities and collaborations, of course, enrich the DOE research program, with no additional support required from DOE. I estimate that 30-50% of the research carried out in my own program is in collaboration with UCLA faculty who are not members of the LBES.

All of the principle investigators in our Division participate in the teaching and administrative programs of their respective academic departments. As an example of the extensive interaction that occurs in our academic setting, I am Director for Basic Research Programs of the UCLA-Jonsson Comprehensive Cancer Center. UCLA compensates the LBES program for our teaching contribution. However, the value to us of our participation in UCLA's graduate educational programs far exceeds this small university financial compensation to the LBES. Probably the most important contribution this interdigitation with the academic programs makes to the LBES is our access to a pool of Ph.D. graduate students and postdoctoral scholars. These individuals are our most successful laboratory workers; intelligent, motivated, idealistic and goal-oriented. Moreover, a variety of university, state, private and federal non-DOE funds are available to support these scholars-in-training in their research while they carry out doctoral and postdoctoral work in our DOE programs. The research of graduate student and postdoctoral fellows supported by a variety of sources, the extensive physical facilities of the campus, and the availability of expertise and collaboration with our many academic colleagues enhance the productivity of our DOE programs many fold. Our Division's seven research programs constitute a distinct unit, with overlapping research objectives emphasizing environmental effects on basic biological processes. we view ourselves as a specialty unit set in, and integrated into, the university environment.

Examples of DOE-Supported Research Programs in the Division of Biomolecular and Cellular Sciences. The majority of our research programs are concerned with molecular and cellular control of cell division and/or gene expression; i.e., molecular and cellular explanations of how and why cells (1) divide, and (2) express properties that make one group of cells in the body differ from others. Thus we are interested in "basic" problems in biology -- but problems whose answers lie at the core of processes as diverse as embryogenesis and aging, or regeneration and cancer. We use contemporary tools of biochemistry, molecular biology, recombinant-DNA technology, cell culture and immunology (including monoclonal antibody technology) in our programs.

We have tried, when possible, to use as research tools experimental systems in which problems of potential clinical significance can also be addressed. Not, however, at the expense of the most direct approaches to the exploration of fundamental questions. Because exogenous, environmental agents alter cellular growth and normal gene expression, we have used such agents as probes of these cellular processes. Thus much of our work revolves around alterations in basic cellular phenomena as a consequence of exposure to environmental toxicants. Many of these studies focus on the processes leading to the uncontrolled growth occurring as a consequence of carcinogenesis and the consequent alterations in cellular properties (i.e., gene expression) in response to environmental pollutants. Let me emphasize that our main perspective is one of understanding basic, fundamental biological phenomena. To carry out more "directed" research on chemotherapeutic models, dosimetry models, etc., in our research context at this time, with our immediate level of knowledge in these basic areas, would be like trying to mop the floor with the water tap still open. Nevertheless, we have in the past made, as correlates of our basic studies, what we regard as contributions that are important to current clinical situations. We will, no doubt, continue to do so. Over the next several paragraphs I will describe examples from our Division of extrapolations of basic studies which have already lead to important medical contributions, or are likely to do so in the future.

Tumor-bearing individuals suffer extensive weight loss and eventual starvation as a result of mobilization of their body fat. Tumors are able to cause normal deposits of fat to become solubilized and recruited by the tumor, for use in tumor metabolism and biosynthesis, at the expense of the host. One of our research groups has recently demonstrated that many tumors produce and secrete a factor which is able to induce this mobilization of stored body fat. The factor has been found in the blood of cancer patients; attention is now directed primarily toward the purification of this lipid-mobilizing factor (LMF). Purification and characterization of LMF, and elucidation of its mode of action, should allow us to develop means to counteract its action and thus aid in maintaining the status of cancer patients.

Combustion of fossil fuels leads to the release of a wide variety of chemicals, including a group known as polyaromatic hydrocarbons (PAH's). These compounds are a recognized environmental health hazard; several are on OSHA's restricted handling list. Many PAH's are potent carcinogens. Animal experiments have demonstrated, however, that PAH carcinogenicity depends on the genetic make-up of the exposed individual. Genetically distinct mouse strains vary greatly in their susceptibility to tumor formation in response to PAH's. Biochemical and genetic studies have shown that the reason for these strain-specific differences in PAH-induced cancer is that the PAH itself is not the carcinogenic molecule. Instead, a product of the PAH, produced by the action of an enzyme in the animal's tissue, is the actual carcinogen. Thus the cells of the animal must activate the PAH to its "ultimate" carcinogenic form. The enzyme that carries out this conversion is normally present in cells in very low levels. After exposure to PAH's the level of this converting enzyme rapidly rises. The PAH-dependent induction of synthesis of the enzyme that will convert PAH's to ultimate carcinogens varies greatly among genetically distinct strains of mice. Those high in the inducible activity are very susceptible to PAH-induced carcinogenesis (as a consequence of the subsequent metabolism of the PAH) while those with low inducible activities have greatly reduced frequencies of PAH-induced cancer. Recent evidence suggests that human populations vary greatly in inducibility for the activating enzyme, and thus may have substantially different tolerances for PAH-induced cancer.

One of our research groups has developed a cell culture system in which homogeneous populations of cells can be isolated that are altered in the various steps in the process of PAH-carcinogen recognition, enzyme induction and metabolic conversion. Using these variant cell lines, the events constituting the pathway of induction of the enzyme that converts the PAH's to the ultimate carcinogen can be worked out, as well as the mechanism of the conversion. Using recombinant DNA procedures coupled with cell culture, this system will be used to clone the human gene directing the synthesis of the enzyme (aryl hydrocarbon hydroxylase) that catalyzes the production of ultimate carcinogens from PAH's. We anticipate that we will soon understand the mechanism of this induction, and may be able, using contemporary techniques of molecular biology, to screen for and identify individuals who may be unusually sensitive or resistant to environmental PAH's.

Heavy metals are also released into the environment during the combustion of a variety of fossile fuels. Cadmium, a toxic metal that is also carcinogenic, is present and released from a variety of coals. Cadmium exposure leads to the induction of a cadmium-binding protein known as metallothionein. Increased synthesis of metallothionein in response to cadmium is thought by many to be a cellular defense mechanism against heavy metal toxicity. Using recombinant DNA techniques, my laboratory (and others) has cloned the gene responsible for directing the synthesis of this unusual protein. We are now studying the molecular structure of the metallothionein gene hoping that it will both provide fundamental insights into how gene expression is controlled by regulatory agents and also provide information of a more immediate, practical nature on defensive responses to heavy metal toxicants.

Tumor promoters are chemicals, found in our environment, that are not themselves able to induce cancer, but can greatly potentiate the tumor-initiating potential of previous exposure to a carcinogen. Thus after exposure to a low dose of a carcinogen (insufficient in itself to cause a tumor), should an individual subsequently encounter a tumor promoter he or she may develop a cancer. Mice have been exposed to low doses of carcinogen, which will not cause tumor formation. One year later (a third of a lifetime) when the animals are exposed to a tumor promoter, they subsequently develop cancer within six to ten weeks. Cumulative effects of exposure to carcinogens may, therefore, be "called out" if, at a later time, an individual is exposed to a tumor promoter. I believe development of methods for identifying tumor promoters and understanding their modes of action are as important as identifying and understanding carcinogens. Identification of tumor promoters has previously required time-consuming, expensive animal experimentation. We have now used a cell culture approach, coupled with genetics, which indicates in only three days whether an agent is a member of one particular class of tumor promoters. By using this analysis we should be able to identify those agents most likely to be positive in the definitive, albeit expensive, animal tests. The use of the altered cell culture lines we have developed should also provide insight into the fundamental cellular processes perturbed by these potent environmental agents.

A number of our research groups have applied immunological techniques to problems of tumor diagnosis and monitoring. Mortality from prostate cancer is second only to lung cancer in men. My own laboratory, in collaboration with the Kaiser Hospital system, has developed a serological test for the presence, in blood, of a unique protein produced by the prostate gland. Patients with cancer of the prostate have elevated circulating levels of this protein. This test is now commercially available and is widely used by physicians in the screening, diagnosis and monitoring of prostate cancer.

We have recently discovered, in collaboration with the departments of Surgery and Pathology at UCLA Medical School, that a protein previously thought to be present only in the brain is also present in over 95% of malignant melanoma tumors. (This coincidence occurs because the two cell types -- the brain glial cell and the melanocyte -- are derived from the same embryonic tissue). Using specific microscopic immunochemical tests for this protein the surgical pathologist can now recognize small numbers of metastatic melanoma cells in sites distant from the original cancer. The ability to distinguish these melanoma metastases from other lesions at distant sites can help the physician to determine the subsequent mode of therapy.

Most recently one of our research groups, using monoclonal antibody technology, has identified a molecule that is greatly enriched in the cells of a particular form of brain tumor. Current studies are directed towards the use of this monoclonal antibody in identifying the chemical nature of this brain tumor-associated antigen. Subsequently, the antibody may be used for diagnosis of the tumor, for monitoring for body burden, and for evaluating various therapeutic regimens.

We have had previous experience in coupling potent toxin molecules to antibodies and growth factors, producing cell-specific "magic bullets". These reagents are designed to preferentially kill target cells carrying specific surface antigens or hormone receptors. We are now carrying out model studies to determine how efficiently such "heterotoxins" work in animals. Once we have optimized these studies we hope to develop "immunotoxins" -- portions of potent toxins chemically coupled to monoclonal antibodies directed against tumor-associated antigens -- as another component of combined chemotherapy for specific types of cancer.

Optimal Productivity in our DOE Program: Let me begin this portion of my statement by emphasizing that (1) we have an excellent situation in which to carry out our research, and (2) that the DOE program, particularly in the development of our own facility, has been administered in an extraordinary fashion. Our relationship with the administration at OHER in Washington has been excellent; I have found them to be helpful, responsive, critical in a constructive way, and supportive of our needs. The particular "needs" that I want to discuss with you are beyond their control, and stem from the organizational structure and funding mechanism. Let me also add, at this point, that these comments apply not only to LBES, but to other DOE laboratories and, to some degree, to the support of research in general.

Research productivity is based, first and foremost, on the presence of trained, creative scientists. The physical plant is of course necessary; the carpenter can't work without his tools. But it is active, inquiring, motivated students, technicians and research fellows that produce the results. A research program is not a single experiment -- it is a sustained, long-term project whose tactics may be shifted by day-to-day or week-to-week events but whose strategies and goals remain relatively constant over periods of several years. Continuity is of great importance; the training, skill and experience of a researcher who leaves the program requires an enormous investment -- financially, intellectually and temporally -- to replace. Because DOE funding is on an annual basis, the individual programs are funded in a similar fashion. Consequently, we must construct our individual research program budgets annually, often near the beginning of a fiscal year and, occasionally, within that fiscal year. This uncertainty in the budgets for specific research programs necessarily makes them less efficient, since we cannot plan very far in advance the complete staffing of our research teams. The development of a budgeting program that defines units of research support for three to five years would, I believe, result in greater productivity and require considerably less administrative activity. My own experience with research programs in which commitments are made in three to five year increments (either from charitable organizations or from other federal agencies) has certainly been consistant with this position; I have been able to devote more time to the scientific objectives of the work and less to its administration. The continuity of the research effort has inevitably benefited the program.

I will use a final paragraph to comment on the impact of the proposed FY1984 budget. I hope I have spent enough time emphasizing examples of the individual acts of creative insight that lead to increased scientific knowledge to indicate that there is no direct correlation between dollars spent and research accomplishments. Nevertheless, verification of scientific hypotheses is not simply the result of inspiration; it requires the perspiration of repetition, confirmation, alternate experimentation, etc. Biomedical research is skilled-labor intensive; it requires long hours of laboratory bench-top effort. Current projections for the DOE FY1984 budget include a 25% reduction in the research support for the Division of Biomolecular and Cellular Sciences at LBES. I do not want to cry wolf with you; our programs can, and will continue to achieve most, although perhaps not all, of our goals. But not in the same time span. The ideas and insights that are the foundation of scientific accomplishment will not occur less frequently with a smaller budget, but their experimental verification or refutation will take longer. We will necessarily take longer, with fewer skilled associates, to test the alternate hypotheses and carry out the verifying experiments that are a part of moving science forward in a believable, substantive fashion. The problem presented by a reduced 1984 budget is, in a sense, primarily quantitative; my colleagues and I are committed to our scientific objectives in lifetime increments, not in fiscal years. Our budgets will determine to some degree the speed with which we progress -- an issue of great practical and social importance -- but not our pursuit of the objectives.

Mr. **Scheuer**. Thank you, Dr. Herschman, for your very excellent testimony.

Now for our last witness and then for some questions and answers after that.

Dr. Richard A. Griesemer, Oak Ridge National Laboratory.

STATEMENT OF DR. RICHARD A. GRIESEMER, OAK RIDGE NATIONAL LABORATORY, OAK RIDGE, TENN.

Dr. **Griesemer**. Thank you, Mr. Chairman.

Thank you for the opportunity to comment on the Department of Energy's research program in cancer research. I think it desirable in proceedings like this to say a little bit about the nature of the problem. How big is the cancer problem? I am sure that everyone here is aware that cancer is certainly a major disease problem in this country. The statistics are particularly frightening, that is, this year 800,000 people will be informed that they have cancer. Another 400,000 people will be diagnosed as having skin cancer, and while that's not quite as serious because many of them can be successfully treated, it is still a very significant large number of people who will have to deal with the threat of cancer. Another 50,000 people will be told that they have precancerous changes in their tissues. Most of those are women who through pap smears and biopsies will learn that there are changes going on in their cervix that need some kind of treatment. One and a quarter million people this year will have direct experience with cancer. One in four of us will develop cancer in our lifetimes, and there is scarcely a family in the country that has not had experience with an immediate family member who has cancer. It is a very significant problem. It is the second leading cause of death as I am sure you all know. While the statistics themselves are frightening, what is not told by the statistics is the suffering and the anguish that goes along with cancer. Cancer is the most feared of all diseases, something that millions of people dread. They see it as a relentlessly progressive disease that disfigures, is painful, and ultimately fatal. That's not altogether true, fortunately, about half of the people who develop cancer this year will be successfully treated, but nevertheless it is a major fear which has a great impact on our well being and how we feel about ourselves and how we conduct our lives.

In addition to all of that, there is an economic burden. It is not generally recognized how great the economic burden of cancer is. My estimate, based on NIH statistics, through last year, is that $50 billion are lost to cancer each year in this country. Nearly $20 billion goes for health care for those people who are unfortunate enough to have cancer. The cost of health care is going up about 11 percent a year, so this is an increasing figure with relatively little hope that the trend will be reversed.

In contrast to the cost of cancer, the amount that the Federal Government spends on cancer research is very small. About $1.25 billion or about 2½ percent of the annual economic cost goes to cancer research. About 80 percent of that is administered by the National Cancer Institute.

The Department of Energy's program is relatively small. For experimental studies in 1982 the Department of Energy administered programs valued at $27.3 million. They had in addition some studies that are difficult to cost out but it is a relatively small portion of the effort.

Some of my fellow witnesses have addressed the role of the Department of Energy in cancer research and they have talked about radiation carcinogenics. I would like to speak just very briefly about chemical carcinogenics.

The Department of Energy is the lead agency for two kinds of research. Research in radiation carcinogenesis and research on complex mixtures of chemicals because the substances that are of interest, energy related substances, to the Department, tend to be complex mixtures of chemicals, with several thousand ingredients in a single substance.

If we listen to the news media we get the impression that we're surrounded by a world of chemical carcinogens and it is unavoidable, and we are going to be exposed to a great number of them. The news media does not report about the chemicals that are not carcinogens. Titanium oxide which is found in paint is not a carcinogen. You don't hear about that. What you do hear about are scare stories.

Let me provide a little perspective. There are roughly 7 million chemical substances known. Of those some 70,000 are important in commerce in the United States. Very few of those have been tested to see if they can cause cancer. Only about 600 have had any degree of testing to give us any kind of data at all. Of those, about one-fourth of them, 160 have some evidence for carcinogenesis. That means even when we deliberately test substances that we think might be cancer producing, three-fourths of those turn out to be not cancer producing, and a small number are. If one combines human data with animal data, one is left with 30 compounds or industrial substances that are considered to be known human carcinogens and another 60 that are probable human carcinogens. So the world of human carcinogens that we live in is something less than 100 substances. The vast majority have never been tested and we don't know anything about them.

We then have to address energy-related substances—synthetic fuels, for example—where there are mixtures of thousands of chemicals, some of which are known chemical carcinogens. It becomes very difficult to test them. We have to develop methods and validate the methods for testing and the Department of Energy has really embarked on a major activity of investigating chemical mixtures which other agencies do not share. The vast majority of other work in cancer research deals with single substances that are relatively pure.

I'll give one example of discoveries in the Departments work thus far. Virtually all of the liquid coal and liquid shale-oil samples that might represent alternate energy sources cause skin cancer. We have discovered through further investigations that it is possible to separate out the cancer causing activity by physical methods or even to abolish it by chemical methods so that safe products can be made. I think we are very fortunate that the developing synfuels industry has slowed down so that medical research can start to catch up with the need.

Last, I would like to mention something about the impact of the budget changes on the National Laboratories and specifically on the Oak Ridge Laboratory. I provided in the written testimony a graph that describes the amount of funds that would have been required to maintain the program I directed from 1978 to the present. I have compared that with the funds actually made available. The difference is about an $8 million shortfall. The Department of Energy's funding has not kept up with the cost of living. In addition, the budget problem was compounded by the transfer of funds from the Department of Energy to the Environmental Protection Agency in 1979. Programs and funds were transferred and in 1981 and 1982, the Environmental Protection Agency phased out all those programs. So, a significant amount of work that had been the Department of Energy's work was lost.

The terrible shortfalls in budgets in the Oak Ridge Laboratory have led to a corresponding decrease in the staff. I provided some data in the written document that shows that we have already suffered a 41-percent decrease in staff in a 3-year period.

The proposed President's budget would cause another decrease in staff to 57 percent decrease over just a few years ago. We also support 130 students and visiting professors who don't show up in those numbers. Needless to say, cutting the staff in half reduces the work that can be performed by half. But it doesn't tell you about changes in the ability of multidisclipinary teams of scientists to conduct work.

We have lost internationally known scientists in specific fields that greatly reduces the effectiveness of the remaining staff to conduct research at the forefront. In addition, the instability inspired by these budget reductions threatens the existence of the remaining staff. I think it likely that if the President's budget were to be approved, that none of the key staff would remain.

In conclusion I would say that the Department of Energy needs resources, the people and the facilities in the National Laboratories for its programs. It would be tragic if the synfuels industry developed with the cost of billions of dollars and we learned later that the products were not safe. The laboratory resources are needed by other agencies. NIH, NASA all rely on the facilities in our DOE Laboratories. The resources are needed by the Nation. The cost of cancer and the suffering that goes along with it are recurring costs; without research they are going to continue to recur and escalate as the population rises. Restoration of the budget to the 1982 level, an increase of 21 percent over the proposed budget, will not save the biology division at the Oak Ridge National Laboratory. Just to maintain the condensed staff we need an increase of 50 percent over the proposed 1984 budget. Thank you.

[The prepared statement of Dr. Griesemer follows:]

TESTIMONY PRESENTED TO THE SUBCOMMITTEE ON NATURAL RESOURCES, AGRICULTURE RESEARCH AND ENVIRONMENT of the COMMITTEE ON SCIENCE AND TECHNOLOGY

March 3, 1983
Washington, D.C.

Richard A. Griesemer
Director, Biology Division

OAK RIDGE NATIONAL LABORATORY*
Oak Ridge, Tennessee 37830
operated by
UNION CARBIDE CORPORATION
for the
DEPARTMENT OF ENERGY

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1. I reside at 102 Danbury Drive, Oak Ridge, Tennessee 37830. I received the Doctor of Veterinary Medicine degree from the Ohio State University, Columbus, Ohio, in 1953 and the Ph.D. degree in veterinary pathology from the same institution in 1959. I am a diplomate of the American College of Veterinary Pathologists. My entire career has been devoted to cancer research.

2. I am presently Director of the Biology Division, Oak Ridge National Laboratory, Oak Ridge, Tennessee, a position I have held since June, 1980. Previously I was Associate Director of the Division of Cancer Cause and Prevention, National Cancer Institute, Bethesda, Maryland, where I directed the Bioassay Program, the federal program designed to detect chemicals that can cause cancer.

3. I am pleased to have an opportunity to comment on the continuing and important contributions of the Department of Energy and of the Department's National Laboratories to cancer research.

Overview of the Cancer Problem

4. When addressing the importance of cancer as a health problem, it is difficult not to focus on the suffering caused by cancer. Cancer is the second most frequent cause of death. According to National Cancer Program statistics, more than 800,000 people in the United States will be diagnosed as having cancer this year. In addition, 400,000 others will develop skin cancer and about 50,000 more will be found to have premalignant changes, mostly in the uterine cervix. Every hour, night and day, an average of 145 people will be diagnosed as having cancer in this country alone. Every hour this year 48 people will die of cancer. More than 420,000 people will die from cancer this year.

5. Everyone is personally affected by cancer to some extent. One in four people will develop cancer sometime in his or her lifetime and there is scarcely a family that has not experienced cancer in a close family member. As examples, one of every 12 women will develop breast cancer; one of every 10 moderate smokers will develop lung cancer; one in 20 men and women will develop cancer of the colon or rectum.

6. The statistics do not tell the entire story. Millions of people live in dread of having cancer some day. Cancer is perceived as being relentlessly progressive, painful, disfiguring, incapacitating, and ultimately fatal. Public opinion surveys invariably report that cancer is the most feared of all diseases. Moreover, many believe that the treatments for cancer are as bad as the disease and are largely useless.

7. Fortunately the public perceptions are not altogether accurate. Not all types of cancer are painful or invariably fatal. Research advances in cancer diagnosis and treatment now permit about half of all cancer patients to be cured. Some types of cancer, notably lung cancer, respond poorly to treatment, however, and continuing research on methods of cancer treatment are urgently needed.

8. Another aspect of the cancer problem that has received too little attention is the economic burden. Few families can afford the cost of prolonged hospitalization and intensive care for an afflicted family member. Not uncommonly, the patient is no longer able to work and pay taxes; the remainder of the family becomes an economic burden on society. According to the National Center for Health Statistics, the economic cost of cancer in

1977 was 35 billion dollars. Years of life lost prematurely were over 6.5 million person years. Lost earnings due to cancer amounted to 26.3 billion dollars. My estimate of the economic cost of cancer for 1983 is 50.348 billion dollars based on projections that account for inflation according to Department of Commerce indices. The most recent available information on medical care costs is from 1980 when 13.6 billion dollars was spent on medical care for cancer patients. Approximately 9.1 billion dollars went for hospital care, 3.1 billion dollars for physician's services, 680 million dollars for drugs, 544 million dollars for nursing home care, and 136 million dollars for other professional services, such as rehabilitation and counseling. Without research the economic costs of cancer will continue to recur and escalate as the population ages. All cancer research is applicable eventually to reduce costs and suffering.

9. In comparison with the economic costs of cancer, the amounts spent on cancer research by federal agencies is small, a total of 1.235 billion dollars in 1981 or about 2.5% of the annual societal cost. About 80% of federal cancer research funds (approximately 980 million dollars in FY-83) are administered by the National Cancer Institute. The Department of Energy's budget for experimental studies in cancer research in FY-82 was 27.3 million dollars.

The Role of the Department of Energy in Cancer Research

10. Historically, the Department of Energy (then the Atomic Energy Commission) had an active cancer research program almost from its inception. Beginning in the 1940's, the development of nuclear weapons mandated a systematic study of the potential adverse health effects of radiation, including

cancer. At risk were workers who manufactured the weapons, the military personnel who transported and might use them, and members of the general population who might be exposed through accidents.

11. The Department's research, conducted in DOE's National Laboratories and in universities, established that radiation is capable of causing leukemia and a variety of solid cancers. The conditions under which radiation might cause cancer and estimates of the degree of risk were then explored experimentally. Experiments with large numbers of animals were necessary to determine the carcinogenic response to radiation at low dose levels. These data now serve as the rational basis for establishing radiation protection standards for people. Because of the Department's research, radiation is the carcinogen best understood by the scientific community. Unfortunately, it is perhaps the least understood by the general public.

12. One of the most important aspects of radiation carcinogenesis studies is as a research model. There is no other carcinogen for which there is such extensive data for human experience and corresponding experimental data in animals. Together they make it possible to develop and validate methods of extrapolation from experimental results to human risk. Such methods are essential if both safe and economically sound standards are to be set for exposures to the many agents to which we are all exposed. Studies of radiation carcinogenesis are important, too, to the understanding of cancer, in general, and have provided much of what is known about the mechanisms of cancer.

13. More recently, the Department's broadened mission to develop alternate energy sources, including synfuels, has required research into the

potential chemical causes of cancer. Synthetic fuels derived from fossil fuels are mixtures of thousands of chemical substances. The Department of Energy's research has shown that the industrial processes originally developed to produce synthetic fuels from coal or shale oil are likely to make products that cause cancer of the skin. Supporting evidence comes from a study in the 1950's of the nation's only operating synfuels plant in which some of the workers developed skin cancer after exposure for only a few years. Current research indicates the feasibility of modifying the industrial processes to produce safe products.

14. Cancer research sponsored by the Department of Energy to meet agency needs complements cancer research conducted by the National Cancer Institute. In broad terms, the Department of Energy is concerned with the possibility that energy-related substances may cause cancer. The National Cancer Institute is concerned with the causes of cancer in general and with the diagnosis, management, and treatment of cancer. To fulfill their missions, both agencies must necessarily deal with the mechanisms by which cancer is produced. The Department of Energy is the lead agency for research on radiation carcinogenesis, on complex mixtures of chemicals that cause cancer, and on the importance of chemical interactions in causing cancer. Identification of the causes of cancer is the key to the Department's goal, that of preventing cancer from energy-related substances.

Cancer Research at the Oak Ridge National Laboratory

15. The Biology Division of the Oak Ridge National Laboratory began cancer research with radiation in 1947, 36 years ago. To understand the possible interactions of radiation with chemical substances in causing cancer

and to compare cancers caused by radiation with those caused by chemicals, research with chemical carcinogens was also undertaken in the 1960's. Because of the possibility that radiation caused cancer indirectly by activating cancer-causing viruses, a third dimension, viral carcinogenesis was later added to what became a comprehensive experimental program at the Oak Ridge National Laboratory on the causes and mechanisms of cancer.

16. In 1963, 20 years ago, a joint cancer research program between the National Cancer Institute and the Atomic Energy Commission was established at the Oak Ridge National Laboratory. The National Cancer Institute contributed to the construction of buildings for the safe handling of chemicals and viruses. Through interagency agreements, the National Cancer Institute support of cancer research operating costs at the Oak Ridge National Laboratory soon reached a level of about 2 million dollars per year and has remained fairly constant to the present time. In 1965 in conjunction with the University of Tennessee, a graduate school was established at the Oak Ridge National Laboratory making it possible for students to receive interdisciplinary research training leading to the Ph.D. degree in cancer research. Predoctoral and postdoctoral students receive stipends from training grants awarded by the National Cancer Institute to the University of Tennessee and the Oak Ridge National Laboratory.

17. The resources available at the Oak Ridge National Laboratory and at other Department of Energy Laboratories for cancer research and research training are considerably different from those in universities. First and most important are the assembled multidisciplinary teams of scientists in the National Laboratories. Cancer research requires expertise in a great many

fields including radiation biology, chemistry, virology, laboratory animal medicine, immunology, genetics, pathology, and statistics. By focusing team research on the disease problem, the Department of Energy's National Laboratories are organized optimally for research in contrast to universities which are organized around specific disciplines to meet their primary mission, teaching. Another important resource in National Laboratories are facilities for housing large numbers of experimental animals under controlled environmental conditions and free of animal diseases. Since cancer is a disease that often appears late in life, it is necessary for some experiments that the animals survive for several years until the cancers form. If the results of the experiments are to be used for regulatory purposes, it is necessary that the experiments meet accepted national and international design criteria and that they are conducted in accordance with the Good Laboratory Practices Act. Few laboratories in the private sector meet these requirements. Among the major equipment items available in National Laboratories are reactors, the sources for radiation in cancer experiments. Facilities are available in which large numbers of animals can be maintained during protracted exposure to radiation at low dose rates in keeping with the way in which humans are exposed. Another advantage of research in National Laboratories is the security of the operations which makes possible classified work on problems that are in the national interest.

Highlights of Cancer Research at the Oak Ridge National Laboratory

18. A few examples of research accomplishments selected from thousands of experiments at Oak Ridge National Laboratory may serve to illustrate the importance of cancer research in the Department of Energy's National Laboratories.

19. Radiation protection standards have a huge economic impact. The lower the allowable exposures, the greater the cost of protection. The single most important set of data on the quantitative risk of cancer from radiation exposure comes from studies of survivors of the atomic bombings in Japan. These studies, supported totally by the Department of Energy prior to 1975 and shared on a 50/50 basis with Japan after 1975, provide useful data at high doses. Few data exist from human studies, however, on the risk from cancer at the lower dose ranges that are now of concern. Estimates of risk are derived instead from mathematical extrapolation or better from experiments in which the cancer response to various low doses and dose rates can be determined. In concert with scientists in other National Laboratories, investigators at the Oak Ridge National Laboratory conducted animal experiments using thousands of mice and confirmed that linear mathematical extrapolation from high doses overestimated the effects at low doses. The savings from not having to reduce the radiation protection standards are estimated to be more than 3 billion dollars per year. The experimental studies also showed that all the life-shortening from low doses of external radiation can be attributed to the increased incidence or earlier onset of cancer rather than to other suspected causes such as brain damage or premature aging.

20. In contrast with x-radiation, cancer risk estimates for neutron exposures are in a state of uncertainty. Atomic bomb survivor studies appear useless for this purpose. Current research in animals at the Oak Ridge National Laboratory indicates that the form of the dose-response curve for neutrons is linear at low doses with a bendover at higher doses, but not a continuous bending. These findings have set the stage for model development

and validation, which will eventually provide the basis for neutron protection standards. The Oak Ridge National Laboratory is one of two laboratories in the United States with the nuclear reactors that allow this work to be performed.

21. In synthetic fuels research, scientists in the National Laboratories, including the Oak Ridge National Laboratory, have discovered that the vast majority of coal- and shale oil-derived liquids cause cancer when applied to the skin of mice. This finding might prevent acceptance of new products by consumers. Additional research, however, has revealed that the cancer-causing activity can be separated from non-carcinogenic components by physical separation techniques and that the carcinogenic activity itself can be abolished by chemical means, such as treatment with hydrogen. The present slowdown in commercialization of synthetic fuels thus has had the unexpected benefit that it provided time for ways to be found to modify the industrial process so that safer products can be produced.

22. Cancer is a multi-stage process. After exposure to a carcinogen, the initial events in cancer formation tend to be alterations in the genetic materials in cells. Later events in promoting the growth of cells with altered genetic information into cells with the properties of cancer cells are caused by substances that don't necessarily act on the genetic material. The identity of the latter substances, known as cancer promoters, are largely unknown except for the skin and are the subjects of intensive searching at the Oak Ridge National Laboratory. Because energy-related substances may be inhaled as well as deposited on the skin, Oak Ridge National Laboratory scientists have directed much of their attention to the respiratory tract.

Methods have been developed recently at the Oak Ridge National Laboratory to propogate normal human respiratory epithelial cells in rodents in such a way that it is now possible for the first time to search for gaseous or liquid substances that can promote cancer in the human respiratory tract.

23. Recent developments in molecular biology and genetics have led to enormous breakthroughs in concepts and methods to understand the cancer process. It is now known that normal cells contain genetic information analogous to that in RNA cancer viruses. If the genetic material in normal cells is rearranged and made active either by chemical or physical (radiation) effects or by insertion of portions of so-called cancer viruses, the cells become cancer cells. In such experiments at the Oak Ridge National Laboratory a unique gene was found in mice that is associated with myelogenous leukemia. The single gene is found on a particular chromosome in non-leukemic mice but is capable of moving to other sites and producing many copies of itself, resulting in leukemia. Myelogenous leukemia is of particular concern in populations exposed to radiation.

24. It is not possible to test all of the 70,000 chemicals of commercial importance for carcinogenicity. Definitive detection of cancer-causing properties can only be done at present in expensive lifetime experiments in animals. Thus far only about 600 suspected substances have been tested reasonably adequately in animals for cancer, and some evidence for carcinogenicity has been found for about 160 of them. According to the International Agency for Research on Cancer, 30 compounds or industrial processes are now considered carcinogenic for humans and another 60 are considered probably carcinogenic. Rather than test all of the chemical substances, Oak Ridge

National Laboratory scientists and former Oak Ridge National Laboratory scientists have investigated the possibility of using information on the structure of chemicals along with pharmacologic and mutagenic (damage to genetic material) activity to predict carcinogenicity. For example, the analysis from a variety of experiments over nearly ten years on a subclass of 140 N-nitroso compounds (nitrosamines) has just been completed. The results, which fill a book (in press), lead to many useful generalizations which greatly reduce the need for further testing of this group of compounds. They also emphasize the limits in using mutagenicity assays as predictors for carcinogenicity for this group of compounds -- a clear indicator that this type of test, commonly used in industry, is likely to be inadequate by itself for regulatory purposes or to guarantee the safety of workers.

Recent Funding History for Cancer Research in the Department of Energy's National Laboratories

25. Unfortunately, the Department of Energy's contribution to cancer research (and to all of biomedical research) has been declining since 1978. The changes in Department of Energy funding at the Biology Division, Oak Ridge National Laboratory (Figure 1) are representative of changes at all the National Laboratories. If one applies annual Department of Commerce Gross National Product deflators to the 1978 budget and beyond, the Department of Energy budget adjusted for the cost-of-living for the Biology Division, Oak Ridge National Laboratory, in FY-83 should be 18.459 million dollars rather than the budgeted amount of 11.780 million dollars. The shortfall is even greater in FY-84 (8.39 million dollars), illustrating a major funding problem. Not all of these funds are earmarked for cancer research but the total biomedical research budget must be considered because many areas of work

including genetics, molecular biology, and biochemistry are integral parts of the cancer research efforts, even though they are not specifically identified and budgeted as such.

26. Major milestones in the decline of Department of Energy funding of cancer research took place in 1979 and 1983. In 1979, 14.1 million dollars of Department of Energy funds and programs were transferred to the Environmental Protection Agency. A few years later in 1981 and 1982, the Environmental Protection Agency phased out virtually all of the transferred programs (along with what had been a 12 million dollar pass-through program), resulting in the loss of a significant portion of what had been the Department of Energy's biomedical programs. In FY-83 the biomedical research programs received an overall reduced budget of 11%. Funds for carcinogenesis were reduced proportionately. The President's proposed budget for FY-84 reduces the budget by an additional 7.3% below FY-83. Experimental studies in cancer research would receive 21.6 million dollars, a 21% decrease from FY-82.

27. Most of the cancer research at the Oak Ridge National Laboratory is conducted in the Biology Division. Not included in Figure 1 are research support and collaboration in analytical chemistry, bibliographic searching, exposure monitoring, and risk assessment, all of which are administered in separate divisions at the Oak Ridge National Laboratory. Funding in FY-81 did not keep up with inflation and was further offset by loss of funds that had been transferred from the Department of Energy to the Environmental Protection Agency. The reduced budget caused a reduction-in-force of 42 staff members or 12% of the staff (Figure 2). Funding in FY-82 from the Department

of Energy similarly did not keep up with inflation and again was offset further by loss of EPA transfer funds. The reduction-in-force in FY-82 gave a total reduction of 127 of 350 staff members in two years. Other extreme measures were imposed to save costs, such as mothballing buildings. An international symposium, the 36th in an annual series, was cancelled. For FY-83, the reduced budget will maintain all but 18 of the remaining staff members but the proposed President's budget for FY-84 would result in the loss of a larger group of 54 more staff members by the end of FY-83 (a 57% loss of personnel in three years).

Impact of Current Budgets on Cancer Research in the Biology Division, Oak Ridge National Laboratory

28. Budget reductions that reduce a group of scientists by 57% in three years obviously decrease the scope of activities by more than half. What may not be so obvious is that the mix of specialists that comprise the interdisciplinary teams is also greatly altered. For example, only two of seven pathologists remain on the staff. Given the uncertain and unstable budgets of recent years, several scientists of international stature have voluntarily moved to other institutions. Recruitment of replacements is impossible under the circumstances. In addition, by the end of FY-83, 85% of the postdoctoral students will be gone and not replaced.

29. As the size of the staff and the scope of activities decreases, the fixed costs of operation become proportionately higher. The utility costs, for example, are 30% of the budget in FY-83 and will represent 45.9% of the budget in FY-84. It costs just as much to provide conditioned air for a room containing a few cages of mice as it does for a room full of mice. The unit costs for mice have tripled in four years (Figure 3) and are so high now that

the Division is hindered in obtaining research support from other federal agencies.

Research Needs

30. It is essential that Department of Energy studies in progress on the carcinogenic effects of neutron radiation be intensified. To establish realistic radiation protection standards, it is necessary to have data on responses to low doses and on the relative biological effectiveness of neutron radiation. Data obtained at the Oak Ridge National Laboratory, for example, indicate that the mechanism for damage of chromosomes by neutron radiation is different from that by X rays and that the relative biological effectiveness of neutron radiation will likely differ for different species and possibly for different cell types within the same species.

31. Ultraviolet light from sunlight is known to be carcinogenic for skin. Since workers in synfuels plants and perhaps the general public can be expected to be exposed to both sunlight and to chemical substances from fossil sources, the possible additive, synergistic, or antagonistic effects when both reach the skin should be investigated.

32. The development of methods to assess the health risks from mixtures of chemicals should continue. People are exposed to many chemicals yet most cancer research until now has been conducted with single substances.

33. For extrapolation of animal carcinogenicity data quantitatively to humans, it is desirable to know about the comparative rates and pathways of metabolism of chemical substances and about the amounts of active metabolites that reach the target tissues.

34. Research is urgently needed to identify substances that promote cancer development in the internal organs. It is conceivable that thresholds exist for promoting activity and that exposures below those levels can be allowed without risk of cancer.

35. Longer-term cancer research should be designed to take advantage of recent breakthroughs in genetics at the molecular level. Cancer researchers are on the threshold of learning the nature of cancer. It is now possible to learn the effects of radiation or chemicals on cancer genes and on their regulation. Cancer genes can be moved experimentally from cell to cell. Putative cancer genes can be synthesized in the laboratory and studied. Scientists in the Department of Energy's National Laboratories are in a premier position to contribute to this subject because each of the comprehensive National Laboratories has an active research effort in genetics. In fact, the Department of Energy's National Laboratories constitute the federal government's major resource in genetics research. Elucidation of the nature of cancer would lead to enormous strides in prevention and treatment.

36. Additional support should be provided to exploit another newly developed research tool, monoclonal antibodies. By fusing cells that produce useful substances such as antibodies with cells that are immortal (cancer cells that can be propagated indefinitely), it is possible now to produce unlimited quantities of substances such as antibodies with specific affinity for components of cancer cells. Such reagents will be useful as diagnostic tools (to find small metastases, for example) and for delivering therapeutic agents to the cancer cell. The specificity of the antibody is analogous to a zip code that sends the antibody to the correct address, the cancer cell.

wherever it is in the body. Scientists can attach substances such as radioactive tags to the antibody that can then be used to find cancer cells and to destroy them. Using this technique, scientists at the Oak Ridge National Laboratory have already cured animals bearing transplanted lung cancers. Although not unique to National Laboratories, monoclonal antibodies are important new research tools required in all cancer research institutions.

Resource Needs

37. The cancer research activities (and indeed all of the biomedical research activities) in the Department of Energy's National Laboratories are in danger of extinction. Declining and unstable budgets over the last decade have not only reduced the scope of activities but have introduced such uncertainty that key scientists are leaving the Laboratories. The brain drain is close to the point where critical masses of scientists will no longer exist. Concomitantly, cost-effectiveness has been reduced as the fixed costs of operating government facilities become a larger and larger proportion of the budget.

38. A number of agencies, including the National Institutes of Health and the National Aeronautics and Space Administration, depend on the radiation facilities at the National Laboratories. For example, studies of reactor fission neutrons, essential for protection standards, can be done only at two National Laboratories. Studies of heavy ions, which are of importance to the National Aeronautics and Space Administration, can be carried out only at Lawrence Berkeley Laboratory. The research experts in radiation and the installations themselves, including the research nuclear reactors, accelera-

tors, and Co exposure facilities, are national resources. If these research teams or the facilities are lost, they will be well nigh impossible to replace. The budget restrictions have already had an impact on the use of these facilities. Further budget reductions will result in the loss of these national facilities and a dispersal of the diminishing number of experts.

39. Declining Department of Energy budgets in recent years have forced greater dependence on support from other federal agencies. At the Oak Ridge National Laboratory, for example, the Department of Energy supported between 80 and 90% of the work for several decades. In recent years, however, the Department of Energy contribution has dipped to as low as 60%. To meet agency needs, it is important that the balance be restored and that the National Laboratories work primarily on Department of Energy problems so that the sense of mission will not be lost.

40. Needed is a return to stable funding to at least the 1980-1981 level with adjustments for inflationary costs for biomedical research. A smaller operation will not meet agency needs and would be so cost-ineffective as to be a poor investment for the government.

41. The special needs of National Laboratories must also be recognized. The cost of housing animals in barrier facilities to protect the experiments is comparable to the needs of physicists for special facilities and should receive separate budget consideration. Most of the facilities were constructed in the 1940's and require extensive renovation and maintenance.

42. I can't speak for cancer researchers in other Department of Energy laboratories but I have every reason to believe that their budgets are simi-

larly inadequate. Laboratories cannot be expected to operate federal facilities and conduct meaningful research programs without adequate support on a continuing and somewhat predictable basis.

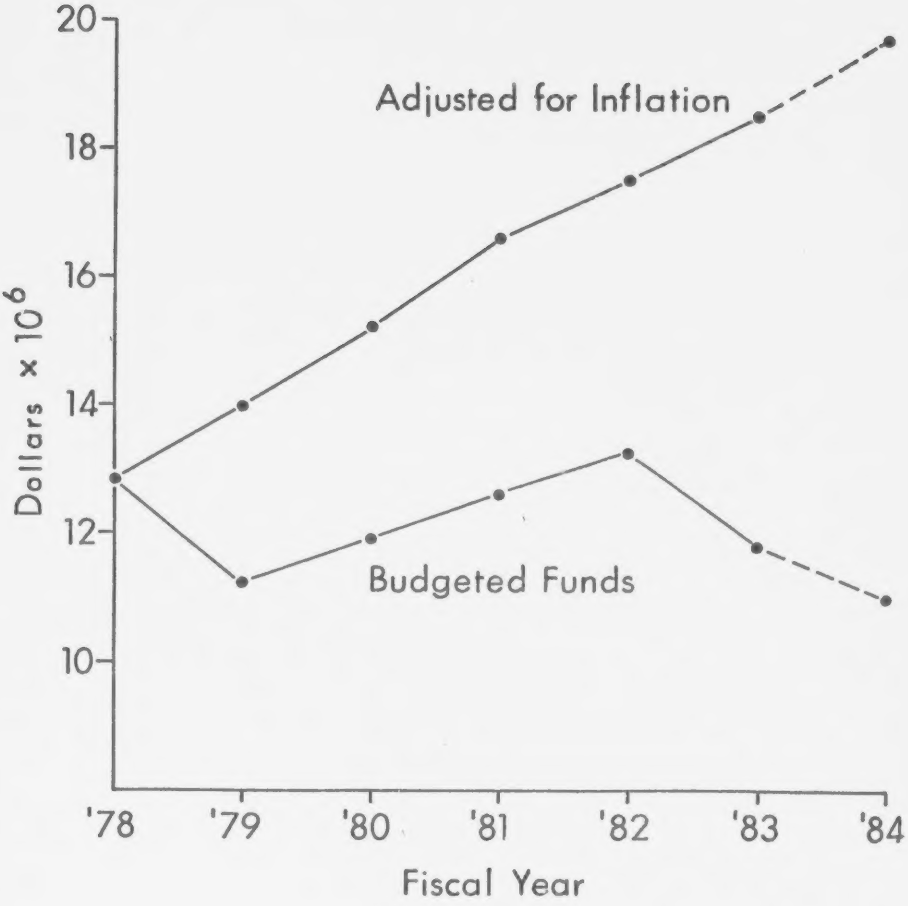

Fig. 1. Recent history of DOE funding for biomedical research at the Biology Division, Oak Ridge National Laboratory. The upper curve has been adjusted for inflation by Department of Commerce GNP annual deflators to indicate the funding levels required to maintain the research programs at the 1978 level of effort.

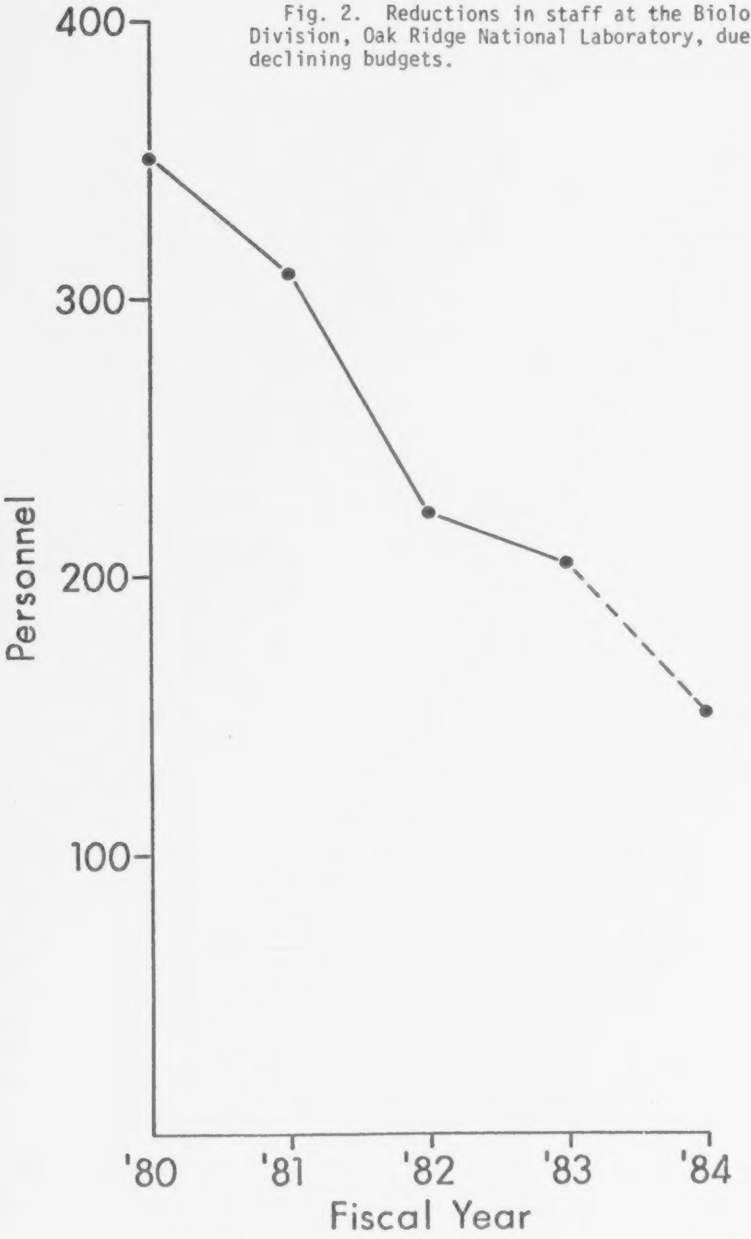

Fig. 2. Reductions in staff at the Biology Division, Oak Ridge National Laboratory, due to declining budgets.

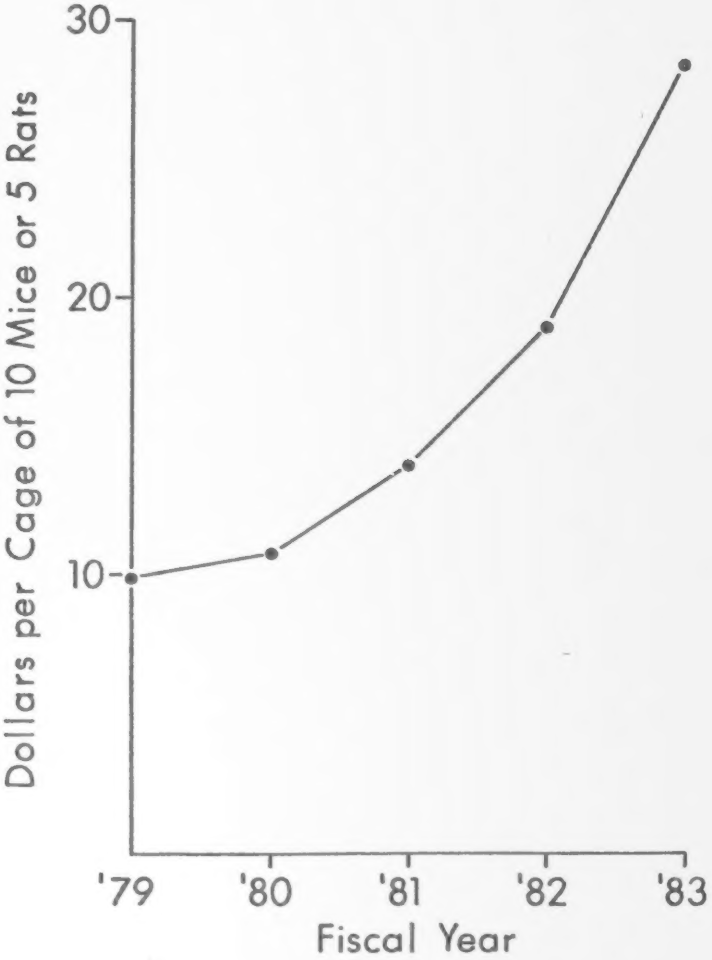

Fig. 3. Increasing monthly costs of maintaining experimental animals at the Oak Ridge National Laboratory illustrate the impact of declining budgets on cost-effectivensss.

Mr. **Scheuer**. Thank you very much, Dr. Griesemer. I can't emphasize how strongly I feel and I am sure my colleagues join with me that you have given us historically important testimony. It is all consistent—each of you have been buttressed by the other three's testimony. It is all a sad story of the disintegration and the gradual decline of our scientific capability in the field of cancer and the fashion in which we are neglecting this research. It is very painful and you have done an outstandingly fine job.

Let me recognize my distinguished colleague, the ranking minority member of this subcommittee, Congressman McGrath of New York.

Mr. **McGrath**. I do appreciate the testimony that we have received today.

Dr. Griesemer, is Union Carbide Corp. going to continue running the Oak Ridge National Laboratory or is Grumman?

Dr. **Griesemer**. The Oak Ridge National Laboratory is a Government-owned facility and the contract is presently being renegotiated. So there will be a new contract in a year or so.

Mr. **McGrath**. And a new contractor?

Dr. **Griesemer**. A single contractor.

Mr. **McGrath**. I have a feeling that one of the corporations in my district might be the contractor.

I have a few questions, none of which deals directly with your testimony—your scientific research. That's what your job is. My job is to talk to you about how we can continue this particular research and the manner in which it is done.

One of the problems, obviously, of the Federal Government today, in budgeting for this kind of research are the multiple agencies that are in the business of providing funds. You recognize that EPA now has a role in this and also the Department of Energy and, of course, NIH and the Center for Disease Control and the National Science Foundation. Generically speaking, is this the proper way to be going about handling the research in this particular area; having it funneled through so many different funds and activities and areas? Or, do we need one institute someplace to handle all of the funding for this particular aspect?

Dr. **Griesemer**. Each of the agencies that you mentioned, has specific needs. The Department of Energy's needs are related to energy-related substances. If the Department of Energy did not have a cancer-research program it would not be conducted by the NIH or the NSF, or the EPA, or any of the other agencies, because each of them has their own interests.

Mr. **McGrath**. But isn't the overall goal our main interest?

Dr. **Griesemer**. The interest is common and we are talking about ways of making progress on many fronts. It is true that research on cancer in a very fundamental way is very very important for cancer in general. In addition, there are very specific needs. We need to know if neutron radiation causes cancer and under what conditions. Who's going to do that? It is desirable that agencies be given very specific missions and that the total work be of a collaborative nature.

I didn't mention, and I don't think it has been mentioned here very strongly, that all of us have collaborative efforts with many of the agencies that you mentioned. At Oak Ridge, we've had a joint program with the National Cancer Institute since 1963. The National Cancer Institute builds buildings, provides operating money, provides training money, which are used in conjunction with the Department of Energy's resources to provide two kinds of activities. General research in cancer and research related toward the specific needs of the Department of Energy. I think that is a logical way of proceeding.

Every dollar spent in cancer research is well spent. None of it will be wasted. Some of it will pay off sooner than others.

Mr. McGRATH. Dr. Herschman, you mentioned a problem in the year-by-year funding. We're probably going to do something tomorrow which we may—or I should say next week—live to regret, regarding budgeting medicare and medicaid and hospital reimbursement on a prospective basis. I am wondering whether the prospective funding would—with a fixed budget for specific activities—would be one way of handling specific experimentation.

Dr. HERSCHMAN. It's a two way street. It depends on the level. My own experience is that the other agencies, from which I have obtained research support for other types of programs and from private organizations, tend to fund on a 2- to 5-year projected program. It's inherent in the way in which their review processes occur as opposed to the Department of Energy.

I have found that it enables us to prescribe our course of action more clearly. We're just able to project over a longer period of time who is going to be there, how long they are going to be there, and what we are going to do. If this type of consideration of DOE funding were applied to at least some of their programs, in the long-term goals, I think, it would benefit the research and the financial status, and it would relieve me certainly of some of the administrative obligations that I have.

Mr. McGRATH. Dr. Setlow, you mentioned that there are so many factors and tendencies: genetic and environmental, toxic waste, the multiplicity of the different chemicals that are in our environment today and other environmental considerations, depending on region and whatever, but there was a relationship between genetics and susceptibility to cancer and different types of cancer. If that's true and all of those are carcinogens, how is it that—how can we come up with standards of parts per billion dioxin in the air and things like that? If all of those factors are true, how can we have an average standard to be approved for everyone in this country?

Dr. SETLOW. That's a very difficult problem. We have to know what the variation is. For example, you are more susceptible to skin cancer than other people. You live out in an area where the people like the sun, and you know this, so you expose yourself accordingly. If we had ways of telling people, be careful, you might be susceptible to certain chemicals then we have a way of protecting—the individual has a way of protecting himself, that's No. 1. No. 2, we know the number of people that are going to be affected by such chemicals, and, therefore, we would have to regulate on that basis. It is obvious we cannot regulate out of existence all chemical and physical carcinogens. That is impossible. The sunlight, you are not going to turn that off. You are not going to turn off background radiation. You are not going to turn off all chemicals, but what you have to get, we have to get, is some kind of an estimate as to the magnitude of the hazard. In order to estimate this, we not only have to know what exists in the environment, we have to know what the various susceptibilities of various persons enzymes are. This is a study that is just starting to bear fruit. If you want me to talk in the wild blue yonder, maybe there are ways in which one could predict what would be a good lifestyle, so that we might not be so susceptible.

Mr. McGRATH. Let me just follow up then by asking you whether it is the role of your research or the role of the Department of Energy, or any of the Federal agencies, or any entity to establish standards of parts per billion in the air of dioxin?

Dr. SETLOW. I happen to be in the position of having answered that question in my own research. My research and that of the Biology Department is devoted to trying to find out how things react and what the data really are. Then we have to really leave it up to someone else such as Congress and other regulators to factor in all these things and to say what's hazardous or not.

Mr. McGRATH. We're very qualified to make these kinds of decisions.

Dr. SETLOW. We will attempt to help.

Mr. McGRATH. Which leads me into my last question regarding research and its application.

It seems to me, given all of the statistics that we have, all of the new technologies and new toxic wastes being discovered and everything else that we have, that we do very little in applying this mountain of knowledge that we are acquiring in terms of risks. What is the risk of doing this as opposed to this in order to solve the same problem? We suggest to you as an example—is it more risky for people to dispose of their garbage—we have it and it's not going to go away—by dumping it in a landfill or by burning it in a resource recovery plant? Is it as risky to have four parts per billion of dioxin coming out of a smokestack for burning that garbage, or is it more risky to your health to strike a match to light a cigarette? Those are the kind of things I think we ought to have available—I don't mean that specific thing—to the general public so they can make a risk assessment. They can make a choice as to whether or not—and it would certainly help us——

Dr. SETLOW. If I might try to answer and not really answer those questions because you're asking us to estimate what the biological effects are of very very low levels of chemicals like those in the environment. It is very difficult, if not impossible, to do these experiments.

Oak Ridge has the biggest experimental mouse colony in the world. It cannot answer the kind of question you are attempting to ask.

This is what we call the shape and the response curve. Is there a threshold somewhere? We don't really have the answers to these questions except, and not well, for radiation. In any case we do not have the answers.

Mr. McGRATH. Now we get around to the Catch-22 of it. Without that kind of input—without the setting of some kind of standard by somebody, hopefully not the Congress—without all of that information how do we protect ourselves as individuals, as businesses and corporations from lawsuits? How do we defend ourselves against a utility that might be burning a certain kind of coal when we don't have the information—enough information—to at least set a standard from which they have to adhere? That's the problem as I see it.

Dr. **Setlow**. I think that's the right kind of question. We do not have the information that you wish. Therefore, in part, we guess at the information. The best example that we have is radiation biology. There are standards for radiation but, nevertheless, despite these standards for industrial exposure and for the average population exposure, there are lawsuits going on. In the West people are claiming they were injured from fallout. You can see how complicated this very simple question is.

Mr. **McGrath**. All right. On that specific point.

Last Friday I had a root canal done on a tooth in New York. A dentist came in and he gave me a couple of X-rays to start with and then as the procedure was going on he gave me a few more to make sure the files were in deep enough and I started to worry about the amount of X-ray radiation I was receiving. Then as it was over he took two more. I said, "what were those two for?" He said those two were for the insurance company so they would believe that he got the job done. I looked at him and I said what is the risk to my health for that particular insurance claim? At this point I would just as soon not have those two extra X-rays if they weren't for diagnostic purposes.

Dr. **Setlow**. In the State of New York, he did put a lead apron over you, did he not?

Mr. **McGrath**. Yes; but it wouldn't have protected me from nose cancer.

Dr. **Herschman**. Mr. McGrath, let me just say that the problem you are alluding to is even more complicated because you mentioned the risk of exposure to airborne dioxin, for example, versus a buried carcinogen in isolation. In fact, the problem of combination of radiations is not simply an additive question. The reason I bring it up is because Dr. Griesemer pointed to the problem of the mixed bag of compounds in synfuels, for example, an area that is supported exclusively by the DOE program. I discussed the combination of low doses of carcinogens that can be enhanced by secondary chemicals in the environment. These are, I think, areas that are of particular interest to the Department of Energy because of their unique orientation toward these energy related environmental compounds. I just want to underscore that.

Mr. **McClellan**. I think the line of questions you have been asking—they go to the heart really of the DOE program. The DOE program per se is not directed at developing standards. It does not have within this particular organization specific standards setting responsibility. But an underlying theme is the development of information that allows us to choose between alternatives. Dr. Griesemer in his testimony alluded to some of the work with the synfuels which was of that type, that is, treatment in terms of industrial treatment, altering the process was able to alter the carcinogenic potential of the material. Now we have a choice in terms of determining do we want less carcinogenic material and what will that cost be. In this particular case I think it was generally accepted that that cost was going to be quite low.

In some work that we've done, working collaboratively with a group at the Morgantown Energy Technology Center, we were looking at various alternatives in terms of clean-up systems for coal gasification. Our point again was would the product that was produced, in the terms of the gas, have more or less mutigenic activity associated with it and thus we hope, more or less carcinogenic potential. So I think an underlying theme that is an important part of the program is this choosing between alternatives and allowing us to guide in terms of various technological developments.

One of the points I tried to make in testimony was that we have over the last 5 years, in the terms of a very technology oriented program, identified some of these crucial areas in which we just have enormous gaps in our information. The whole question of complex materials is one which is just not being adequately addressed in terms of any other agencies within the government. It is a central theme within the Department of Energy programs. It was one of the major areas identified in the Nation Academy of Sciences' briefings to the President's science adviser as an area deserving of more attention.

Mr. McGrath. All I am trying to say is with all this research, all the information that we have this Government cannot enforce whatever, except by goodwill, information retrieval that we are able to come up with. It's like a true Catch-22. I want to thank you all for being here as witnesses. It was very informative.

Ms. Schneider. I would like to respectfully disagree with my colleague, if I may, before I ask some questions. I think that the thing these gentlemen were all testifying to relates to two parts I picked up on your remark, Dr. Setlow, in your response that in the setting of standards where is there a certainty how many parts per billion will have an impact and Dr. Setlow said that essentially it has to be guesswork. I think that you need to understand that the reason it is guesswork is because, as these fellows said, they are dealing with two variable dynamics. One is that each individual and the DNA's and whatever within each individual are so different that what affects you may not affect me and vice versa. The second point being, they don't really don't know what the impact will be because of the accumulative activities that are taking place with either one chemical or a multitude of chemicals. Does that pretty much reflect what all of you have been saying? That there are those two variables.

Dr. Setlow. You summed it up very well.

Ms. Schneider. The other point that was made was we set some standards; we come up with some estimate approach to defining what is carcinogenic and what is not. How do we disseminate that information and get it out to the general public? I think that there has been a lot of criticism in this congressional body as to us coming up with recommendations that are often referred to as guesswork, and the obvious specific examples are the cigarette smoking, you know, how many packs of cigarettes does a mouse have to smoke before they develop lung cancer. The same thing with the diet drinks or the material that is put into diet drinks. This information has gotten to the public. The public has been warned about the effects of the Sun for skin cancer and those kinds of things. I guess what frustrates me is the expenditure of these dollars into the research, then the dissemination of information to the general public. The final thing is that the public doesn't take advantage of that information, because we see the continued high incidences of lung cancer, which are believed to be resulting from cigarette smoking.

Now, what I want to do is address it more in your area of energy research. Is the Department of Energy the only Federal agency that is researching the impact of energy-related carcinogens on human health?

Mr. McClellan. The two principal agencies that have been involved in the past have been the Department of Energy and the Environmental Protection Agency. The Environmental Protection Agency's budget for energy related environmental and health research increased to something over 100,000,000 at its peak. That's now been increased and I believe the President's budget proposes $23 million for this year $14 million for acid rain; $7 million for control technology; and $2 million for health effects research. That $2 million is perhaps a misnomer to identify it as true research. It is not gathering of new knowledge so much as it is trying to bring it together in assessment fashion. Certainly I think that's a useful kind of activity but one of our real shortages here is absolute new knowledge information that allows us to really make these—Dr. Setlow referred to them as guesses, if you will—in terms of our standards I think it is best to call them educated guesses. We do the best we can with the information at hand.

I think to characterize the difference between what's happened in the Environmental Protection Agency program and the DOE program, both of which I followed closely, one serving on the EPA's Science Advisory Board, the other as an active participant on DOE's program, is that while the EPA program is—I hope it has not been a prelude, but it has gone down hill steadily year-by-year to a lower and lower level—close to its demise.

Ms. Schneider. Almost nonexistent.

Mr. McClellan. And what we've seen, and I have participated in these activities, scientists do their best to use the information at hand in terms of setting standards developing assessment documents. That is not creating knowledge to fill these voids. That is what the DOE program has been doing; what we're seeing is a sharp reduction in the funding there. My concern is as in the past as we've seen with EPA being simply played out again with DOE, and we would lose a valuable national resource.

Ms. Schneider. I regret that's a bell for a vote and I have about 13 other questions to ask.

Mr. Chairman, is it all right if I proceed until we have to run over there?

Mr. Scheuer. Let me ask one question and then we will proceed for 10 minutes.

I'm going to ask unanimous consent that members be enabled to submit questions in writing and that the record be held open for another 10 or 12 days for the answers to be received.

There being no objections it is so ordered.

Let me ask my question and then I'll yield, the remainder of time.

Dr. Setlow, you mentioned some lifestyle options that would help people minimize their exposure to carcinogenic elements in our environment. I have felt that CAT scanners were great and open heart surgery is great and tertiary hospitals are great, but until we teach the American people that this high technology is not the answer to improving their health outputs, we are not going to improve health outputs very much. We have to get people to take charge of their own health, and that means the avoidance of drugs, avoidance of mind altering drugs, avoidance of tobacco, better diet, more exercise, avoidance of violent situations and the like. What are the things consistent with this point of view—what are the things that each of us can do in terms of lifestyle choices that will minimize to the maximum extent possible, or the danger of our exposure to these carcinogens that are in the environment?

Dr. SETLOW. Of course I have no real answer to that question except one. Stay away from them and two, we do not know enough about our own metabolism that controls our metabolic pathways so that I can tell you what the best thing is to live on to help your metabolic pathways.

Ms. SCHNEIDER. Just going to suggest that he get a lot of rest, good food, and run every morning.

I would appreciate, I guess, as brief answers as possible but if some of you feel that it's necessary to expand upon these answers, terrific, give me a signal because I do want to get through a number of these questions.

Dr. McClellan, I wanted to find out if you know if there are any other nations that are conducting energy research as we are here in the United States.

Dr. MCCLELLAN. I think that the U.S. is the acknowledged leader in the area. Certainly, there are other efforts underway. If we look in the radiation area, traditionally, there have been strong efforts in terms of France, the United Kingdom, Germany to a lesser extent, and the Japanese more recently.

Ms. SCHNEIDER. Do we have any cooperative programs with them now?

Dr. MCCLELLAN. I can't address the formal nature of that. In an informal way I think we have a good degree of cooperation there. We move into the synfuels area, if you will, the fossil-fuel arena, there the efforts again have developed somewhat later than in the United States in terms of Germany and Japan, specifically. I'm thinking of laboratories there. They have been pretty much specifically oriented to some of their unique kinds of problems. For example in Japan the use of methynol/coal slurries.

Ms. SCHNEIDER. Dr. Griesemer, could you tell me have you shared information from Oak Ridge National Laboratory that has come forward on the effects of synfuels on—so far as causing skin cancer—with the Synthetic Fuels Corporation? The reason I ask is, that I guess, we all know that the Synfuels Corporation hasn't, as yet, provided funds or given the go ahead to any project but they are right now in the process of allocating some moneys, and I am concerned that if they allocate those moneys they give it to a demonstration project that has looked far enough ahead to recognize health effects.

Dr. **Griesemer**. Yes. We are in direct communication with them, and I presume all the national laboratories are. We have reviewed all of the research results and summarized them and also recommended areas for research to the Synthetic Fuels Corporation.

Ms. **Schneider**. OK. Thank you.

Dr. Herschman, if there were an individual who was perhaps in the military, went to Nevada during the atomic tests that were being done—I guess there is a group now being referred to as the atomic vets—is it possible now through the research now that you have been doing, and through the tests that you have developed to determine whether or not a given individual is likely to develop cancer?

Dr. **Herschman**. No. Not at this moment.

Ms. **Schneider**. Well, the blood test——

Dr. **Griesemer**. It is possible, however, to remove some tissues from such people, if they are willing and apply tumor promoters in tissue cultures and demonstrate transformation. There's a developing battery of tests that will make that possible, however, they would require the permission of the individual involved to run the tests. There's the additional problem of what do you do with the answer. Tell someone he's a greater risk for cancer? Who's going to pay for his medical care?

Ms. **Schneider**. That's the question that you can't help but ask. My response is why are you doing the research then to identify who is more susceptible to develop cancer than who is not.

Dr. **Griesemer**. We're trying to prevent cancer.

Ms. **Schneider**. But you are preventing it by finding out two things. Who is more susceptible and what are the different types of environmental causes that exist.

Dr. **McClellan**. I think that one of the things that one should not overlook there is it's not just a case of identifying more susceptible from less susceptible. These provide very important tools by which we can actually understand the disease process.

Perhaps one of the great opportunities in terms of biological experimentation is to be able to identify two populations that have clearly different responses. Then if we could understand the basis for that differences that really starts to give us insight into the mechanisms.

Ms. **Schneider**. I, unfortunately, have too many more questions, but I have to run over one last question.

One of you did make some comments about plutonium causing cancer. That is commonly accepted is it, by the research community?

Dr. **McClellan**. Yes.

Ms. **Schneider**. When we talk about levels, what kind of miniscule particles are we referring to? Pieces or specks of dust or smaller?

Dr. **McClellan**. We really have to talk about is the risk to the tissue. There is no question when we talk and the usual terms used are REMS or RADS of radiation dose. There is clear agreement plutonium can cause cancer—lung cancer, skeletal cancer. Where we start to get into areas of disagreement is when we get down to very low levels and the question of whether—how do other materials interact, for example the question of cigarette smoking is interacting with plutonium in terms of lung cancer.

Ms. **Schneider**. I regret I cannot miss this vote and I have found this whole testimony exceedingly informative and enlightening and I only wish we had more time this afternoon.

I thank you for your testimony and I'll be sending you some letters in the mail with more questions.

Thank you very much.

We are adjourned.

[Whereupon, the subcommitted adjourned at 4:14 p.m.]

APPENDIX

QUESTIONS AND ANSWERS SUBMITTED FOR THE RECORD

Questions

Dr. Herschman

Research on Cells

1. On page 4 of your testimony you state, "Many of our studies focus on the processes leading to the uncontrolled growth occurring as a consequence of carcinogenesis and the consequent alterations in cellular properties in response to environmental pollutants."
   A. Are these basic research studies on cell function necessary in order to understand the causes of cancer? If so, explain why.
   B. Are similar basic cellular studies conducted at federal agencies other than DOE? If so, what agencies and what is the level of funding?

Tumors and Body Fat

2. On page 5 you discuss research related to tumors and body fat. Your studies have shown that there is a factor in the blood that mobilizes body fat from normal cells to tumor cells and as a result there is extensive weight loss while the tumor grows.
   A. What is the current status of this research?
   B. What are the future research needs, financial, DOE support, etc., of this program?
   C. Could this research lead to the development of a vaccine to combat this type of tumor?

Combustion of Fossil Fuels and Cancer

3. On page 5 you discuss your research on the relation of chemicals produced from burning fossil fuels that will cause cancer. Your studies have shown that an enzyme in the blood of some people makes the chemicals carcinogenic.

   A. What is the current status of this research?

   B. How widespread is the cancer caused by these chemicals?

   C. What is the level of DOE funding for this research?

Chemical Tumor Promoters

4. On page 7 you indicate that there are chemicals in the environment that promote tumors. These chemicals do not cause cancer themselves but promote cancer that has developed as the result of exposure to a carcinogen.

   A. What are some of the chemical promoters that you have identified? How widespread are they in the environment?

   B. What are the future directions of this research?

Tumor Vaccine

5. On page 8 you discuss the use of monoclonal antibody technology in the study of a particular form of brain tumor. Does this mean that you are working on a tumor vaccine? Could such a vaccine be developed as a result of your research?

Impact of FY 1984 Budget

6. On page 11 you state, "Current projections for the DOE FY 1984 budget include a 25% reduction in research support for the Division of Biomolecular and Cellular Sciences at UCLA."

   A. What impact will these budget cuts have on cancer research at UCLA?

   B. How will this alter long-term research in chemistry?

Responses to questions from Subcommittee testimony on Natural Resources, Agriculture Research and Environment of the Committee on Science and Technology on March 3, 1983

Dr. Harvey Herschman

Research on Cells:

A. Yes, such basic studies are necessary. We cannot cope in a rational way with alterations in control of cell growth unless we understand the process. It's a bit like trying to mop the floor with the water tap open, or explain how an automobile works by looking at its exterior. We can only throw things at cells and record responses if we do not learn the basic molecular and cellular processes governing growth.

B. Yes, similar studies are supported by NCI and NSF. I cannot give dollar figures for their levels of support. However, DOE funding is directed more specifically at not only describing the basic processes, but asking how environmental pollutants alter and effect these processes.

Tumors and Body Fat:

A. Dr. Mead and his collaborators have partially purified the factor, and are trying to characterize it.

B. The primary need is for trained professional investigators; advanced degree researchers and technicians. This program, to be carried out effectively, requires about $150,000 per year gross support. This will fund a professional researcher, a technician and their supply needs.

Tumors and Body Fat (Cont):

C. A "vaccine" is not the correct term. It would lead to the development of an agent that could reduce that debilitating effect of the cancer by preventing the patient from wasting away.

Combustion of Fossil Fuels and Cancer:

A. We are currently trying to isolate and characterize the genes responsible for the production of this enzyme. I believe we should be able to accomplish this goal in the next three years. We will then be able to examine these genes, in molecular terms, to determine what causes them to be turned on and off.

B. It is difficult for me to answer this question, since I'm not an epidemiologist. The first cancer known, with certainty, to be induced by chemicals, described by Sir Percival Pott in 1778, was induced by just such a chemical; the elevated presence of scrotal cancer in chimmney sweeps due to the burning of coal. There are increased levels of cancer in highly industrialized areas that burn these fossil fuels.

C. The level of funding in our laboratory for this program is about $120,000, or $90,000 spendable'after overhead.

Chemical Tumor Promoters:

A. Tetradecanoyl phorbal acetate and teleocidin (from croton plants and fungi) are two such promoters. Our own lab has not, to date, identified new agents; we have been occupied developing a reliable assay system. Their distribution in the environment is not yet well worked out, since their detection has, until recently, been so time consuming and expensive.

Chemical Tumor Promoters (Cont.):

B. We want to develop both a screening program to look for additional promoters, and a molecular research program to eludicate their mode of action.

Tumor Vaccine:

While we would not develop a vaccine we would, hopefully, be able to develop a sensitive assay that will enable us to measure the "body burden", i.e., the amount of tumor still present in the patient after treatments. By coupling toxins to the antibody, a procedure we have pioneered in our laboratory, we might also be able to make tumor-specific toxins.

Impact of FY84 Budget:

A. These budget cuts will slow our research. We will be forced to terminate the employment of skilled technical and professional staff. We simply will not be able to press forward at the same rate. Dismantling a research team in this fashion occurs much quicker than rebuilding it. Putting the money back in later does not replace the lost experience, commitment and specific knowledge that departs with the terminated individual.

B. These cuts will certainly slow our pursuit of our goals. Beyond a certain point they will be stifled, since a critical mass of committed investigators is necessary to make progress. We are, in some instances, approaching such a situation.

Questions

Dr. Setlow

Cancer Studies

1. On page 3 of your testimony you state, "DOE contractors still remain the leaders in radiation biology, which now also encompasses wide areas of chemical carcinogenesis, because a number of chemicals mimic radiation in its effects on DNA."
   - A. What specific cancer studies in chemical carcinogenesis are underway in DOE labs?
   - B. What are some of the most recent advancements in these areas?

Study of Chemical Hazards

2. On page 4 you state, "...the new field of genetic toxicology is so important now in evaluating the effects of chemical hazards in the environment."
   - A. Explain what genetic toxicology is and why it is so important.
   - B. What are some of the applications of this research in cancer studies?

Skin Cancer

3. Your research has made a significant contribution in understanding skin cancer. For example, your work lead to the discovery that some

people have a genetic suspectibility to environmental carcinogens.

A. What are some of the areas in which additional research is needed?

B. What is the present funding level for the skin cancer research program?

C. If the funding level for FY 1984 is increased, how would that lead to benefits to poeple who are susceptible to skin cancer?

Chemical Agents and Genetic Damage

4. On page 6 you state, "Sensitivities to chemical agents often mimic radiation sensitivities." You continue on and indicate that both can cause genetic damage, but at low levels of the agents DNA can repair itself.

   A. How does this research relate to cancer?

   B. What are the applications of this research?

   C. In order to maintain an adequate research program in this field over a long time, what additional funding and support is needed?

Impact of FY 1984 Budget

5. On page 8 you state that, "DOE's present budget estimate for FY 1984 for Brookhaven's research program in biological structures and in cancer research is 11% below 1983...Such cuts would devastate a research program that is generally agreed to be excellent, relevant and appropriate for a National laboratory."

   A. How would such a budget cut impact on the cancer research program in terms of results?

   B. What would be the impact on long-term research? How could this impact on the American public?

Answers to Specific Questions
Posed to Richard B. Setlow

Cancer Studies

1. One page 3 of your testimony you state, "DOE contractors still remain the leaders in radiation biology, which now also encompasses wide areas of chemical carcinogenesis, because a number of chemicals mimic radiation in its effects on DNA."

A. What specific cancer studies in chemical carcinogenesis are underway in DOE labs?

Answer:

At Brookhaven we are investigating the biological effects of carcinogenic alkylating agents, for example, analogues of nitrosamines. We are studying the effects of such agents on human cells in culture and on the abilities of such cells from apparently normal individuals and people with chronic lymphocytic leukemia to repair DNA damage from alkylating agents.

B. What are some of the most recent advancements in these areas?

Answer:

Three unanticipated advances have been made in this field (this is an extension of the material covered in my written testimony, page 6). 1) There is a big variation in DNA repair among apparently normal individuals. 2) Many human transformed cell lines are sensitive to the killing effects of alkylating agents. 3) Cells resistant to alkylating agents are able to adapt to the presence of low levels of such agents in the growth medium by increasing the amount of repair protein. Sensitive cells cannot make more repair protein; and hence, their repair system becomes saturated and inoperative. 4) There appears to be a threshold dose below which there are very small effects because repair is proficient but above which there may be large effects because the repair system is saturated.

Study of Chemical Hazards

2. On page 4 you state, "... the new field of genetic toxicology is so important now in evaluating the effects of chemical hazards in the environment."

A. Explain what genetic toxicology is and why it is so important.

Answer:

Genetic toxicology is the study of the genetic and chromosomal effects of chemicals and radiations on mammalian cells from animals or cells exposed to potential mutagens. The subject is important because it represents a quantitative way of measuring the potential mutagenic effects on human cells.

B. What are some of the applications of this research in cancer studies?

Answer:

There is a close correlation between mutagenesis and carcinogenesis. The mutagenic test systems utilized in studies of genetic toxicology are relatively inexpensive and easy to carry out on cells in culture. Whereas the cancer test systems require large numbers animals treated for long times. In most screening systems for deleterious chemicals one measures genetic toxiologically effects and not carcinogenic effects, because the former is so simple and rapid to do. It would not be possible to do direct carcinogenic studies on all the many chemicals introduced into the environment. A recent one page summary in Nature, Vol. 301, p. 653 (1983), summarizes a National Academy report on "Identifying and Estimating the Genetic Impact of Chemical Mutagens". The article concludes by saying, "What trigger-happy lawyers and their paymasters must be made to understand is that the Environmental Protection Agency has asked an interesting question, that the National Academy of Sciences has given an intelligent answer, and that there is, for the time being, no way of telling what should be done to protect people against the hypothetical hazard of germ-line mutations by chemicals except by the support of basic research." The same comment holds for the quantitative estimate of the hypothetical carcinogenic hazards of chemicals.

Skin Cancer:

3. Your research has made a significant contribution in understanding skin cancer. For example, your work lead to the discovery that some people have a genetic suspectibility to environmental carcinogens.

A. What are some of the areas in which additional research is needed?

Answer:

One area of importance is to measure the susceptibility of different humans to DNA damage and to their abilities to repair ultra-violet damage. It is important to know what the natural variation is among the population of the various repair systems.

B. What is the present funding level for the skin cancer research program?

Answer:

At Brookhaven we are not funded for any specific amount for skin cancer research but are funded for fundamental studies into damage to DNA and how it is repaired and what are the efficiencies of ultra-violet light in transforming human cells in cultrure to the neoplastic state as a result of exposure to ultra-violet radiation. The total funding for such studies is in the neighborhood of $350,000. These sums must pay all salaries, and of course, upkeep for the laboratories and facilities.

C. If the funding level for FY 1984 is increased, how would that lead to benefits to people who are susceptible to skin cancer?

Answer:

An increased level of funding would lead to a more rapid identification of people who are somewhat more susceptible to skin cancer and hence, they could be warned to avoid the mid-day sun, because the sun's rays at mid-day are much more carcinogenic than early in the morning or late in the afternoon. A second benefit would be to the general population since there are tantalizing clues that the time of day during which you receive your sun exposure may be important in determining the carcinogenicity of such exposure. It seems as if exposure in the afternoon may produce appreciably less carcinogenic effects than in the morning because of the different levels of the repair systems that operate in the morning and in the afternoon sun.

Chemical Agents and Genetic Damage

4. On page 6 you state, "Sensitivities to chemical agents often mimic radiation sensitivities." You continue on and indicate that both can cause genetic damage, but at low levels of the agents DNA can repair itself.

A. How does this research relate to cancer?

Answer:

Cells that are defective in the ability to repair DNA damage or cells that repair damage slowly are much more likely to be mutated and to turn into cancer cells than are normal cells that repair DNA damage rapidly.

B. What are the applications of this research?

Answer:

The applications of this research are threefold. 1) Such research is used to identify agents that react with DNA by measuring the amounts of repair that they induce. 2) As I indicated above, in the section on study of chemical hazards, such data may be used to estimate the shapes of the dose response curves for chemical or radiation damage and so predict the effects of low doses from the observed effects at high doses. 3) Such experiments may be used to identify individuals with special sensitivities to chemical or radiation damage or to identify individuals with extraordinary resistances to such agents.

C. In order to maintain an adequate research program in this field over a long time, what additional funding and support is needed?

Answer:

As far as the research program of myself and my collaborators is concerned the additional funding needed is around $200,000 per year.

Impact of FY 1984 Budget

5. On page 8 you state that, "DOE's present budget estimate for FY 1984 for Brookhaven's research program in biological structures and in cancer research is 11% below 1983...Such cuts would devastate a research program that is generally agreed to be excellent, relevant and appropriate for a National laboratory."

A. How would such a budget cut impact on the cancer research program in terms of results?

Answer:

As I indicated in my formal testimony, the Biology Department at Brookhaven must be viewed as an interacting group of investigators interested in both structure and function. Research in one aspect is really useless without the other. Hence, any shortfall in our departmental budget will affect the cancer research program. If our budget were 11% below that in 1983, which budget itself did not keep up with inflation, the department's DOE supported investigators would have to be cut by something between 15 and 25%. Cuts of this magnitude may seem small, but I would estimate that they would lower the productivity by something between 20 and 50%.

B. What would be the impact on long-term research? How would this impact on the American public?

Answer:

The effect would be a harsh one because existing competent investigators would look for other jobs in other fields, and more importantly, younger scientists would see such fields as ones to be avoided. The net impact on the American public would be, that there would be a big decrease in long term research on the effects on the environmental pollutants on humans and the regulatory process would have little scientific base to support it. Thus, one could envisage situations in which the environmental impact would be underestimated giving rise to public health problems or the environmental impact could be over-estimated, giving rise to severe financial penalties for companies engaged in manufacture of particular chemicals.

Chemicals and genetic damage

The US National Academy of Sciences has told the Environmental Protection Agency how to regulate chemicals causing inheritable mutations. But the more urgent need is for more research.

CAN CHEMICALS cause inheritable mutations? the simple answer is "Why not?". For it is well known that chemicals can cause mutations in the somatic cells of sexually reproducing organisms of all kinds. Much human cancer is probably caused by such means. So why should the germ line be immune from chemically caused mutation?

Two conflicting pieces of evidence make the question more interesting than it might at first sight seem. First, there is the surprising evidence, recently accumulated, that the children begotten of people exposed in 1945, at Hiroshima and Nagasaki, to radiation from the earliest nuclear weapons have been remarkably free of genetic aberrations caused by dominant mutations. Nobody knows what the explanation is. Are germ cells unexpectedly resistant to mutagenic influences, perhaps because they are dormant for most of their existence, or is the uterus a more efficient way of distinguishing between unwanted dominant mutations than has hitherto been supposed? That question will be more easily decided when more is know about the occurrence of recessive mutations among the descendants of the people exposed to the first nuclear explosions. Meanwhile, it remains a matter of public record (see *Nature* 154, 81; 1944) that the simple and naturally occurring chemical allyl *iso*-thiocyanate can cause inheritable genetic mutations in *Drosophila*. More recently, there have been reports that defoliants contaminated with dioxin and used in the recent war in south-east Asia have scattered inheritable genetic damage through the exposed population.

So it is natural that the US Environmental Protection Agency, required by law to anticipate (and to prevent) such occurrences, should have asked the US National Academy of Sciences to suggest how the potential of particular chemicals to cause germ-line mutations can be assessed without too much administrative trouble (and cost). The academy's Committee on Chemical Environmental Mutagens, itself an offshoot of the Board on Toxicology and Environmental Health Hazards, one of the dependants of the academy's Commission on Life Sciences, has now dutifully obliged*. The committee suggests that if the Environmental Protection Agency is bent on spotting inheritably mutagenic chemicals before they cause damage, it had better rely on a combination of two diagnostic tests — some version of the Ames test (mutagenicity potential in *Salmonella*, for example) and an assay of potential for causing chromosome breaks in cultured mammalian cells, cells derived from Chinese hamster tissues for example. By all accounts, the agency is not sure how it should respond to this surprisingly pragmatic advice.

What the agency should do is to read the fine print in what is an exceedingly intelligent report. First, it must take the point that most chemicals that affect the life of organisms do so not in their own right but because of their metabolic products. Somatically mutagenic agents such as benzopyrene, for example, cause cancer only when they are converted into epoxides. Obviously, then, no simple combination of an Ames test and something else can be an unambiguous pointer to the inheritable damage that some chemical may do. And false negatives — assays in which a chemical appears innocuous but is not — will be more worrying (because they will not be immediately apparent) than false positives, still one of the major anxieties in the use of the Ames test of mutagenic potential in bacteria as a guide to carcinogenic somatic mutation is mammalian cells. Second, the Environmental Protection Agency must recognize that the telling import of the National Academy report is that it does not point to immediate legislation but, rather, to the need for some sensible programme of research. The goal should be to identify a few cases in which chemicals cause genetic alterations of the germ-line, and then to understand why they occur — and do not occur more often. It should be chastening for all that the paper by Auerbach and Robson, published nearly forty years ago (see above) is still the most often quoted.

Luckily for us all, the National Academy's report embodies a few important pointers to what might be done. The ideal, of course, would be that there should be such a full understanding of what happens metabolically to particular chemicals in mammalian cells (germ as well as somatic cells), and such a full catalogue of possible interactions with nuclear DNA, that the prediction of mutagenicity would be possible. For the time being, however, such an objective is entirely beyond the bounds of what can be attained. So the best hope is that some long-pocketed agency such as the Environmental Protection Agency should support an empirical attempt to discover what there is in common between the chemicals — the list is short — known to be mutagens of the germ-line. The National Academy's committee has several useful suggestions as to how extra resources might be used in such an endeavour — the study of natural repair mechamisms or of the role of mobile genetic elements (transposons) in mutagenesis, for example. But the most urgent need is of some means for tackling a problem that usually goes unstated — that of estimating the true biological damage that may be done by chemical mutagens, allowing for mammalian fetuses prophylactically, so to speak, aborted and for biologically unimportant defects which, when inherited are equivalent to impotence.

None of these questions will be quickly answered, so that the Environmental Protection Agency is right to be saying (for the time being) that it has no specific programme of legislation up its sleeve. For as things are, the legislation on the toxicity of chemicals that already exists for practical purposes allows the use of chemicals that show up positive on a simple Ames test to be regulated. The consequence is that laws intended to control those chemicals that show up positive both on an Ames test and for their capacity to cause chromosome breaks in cultured mammalin cells are likely to be superfluous: culprit chemicals are almost certain to be caught by the net with the finer mesh. Indeed, the procedure that the National Academy recommends is either administratively irrelevant or it amounts to a plea for finding those mutagens of mammalin DNA that are not recognized by the Ames test.

The second course is entirely laudable, and should be followed as energetically as time and resources will allow. The danger, created simply by the agency's expression of interest in this question is the belief that to every problem there should be a matching piece of legislation. What trigger-happy lawyers and their paymasters must be made to understand is that the Environmental Protection Agency has asked an interesting question, that the National Academy of Sciences has given an intelligent answer, and that there is, for the time being, no way of telling what should be done to protect people against the hypothetical hazard of germ-line mutations by chemicals except by the support of basic research.

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* *Identifying and Estimating the Genetic Impact of Chemical Mutagens* (National Academy Press, Washington AC, 1983).

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Dr. Griesemer

Cause of Cancer Deaths

1. In your statement you indicate that "This year 420,000 people will die from cancer."

   A. Do you have any data on how many of these cancer deaths will be caused by energy related technologies?

   B. How many of these cancer deaths will be caused by environmental factors?

   ANSWER: Insufficient research has been conducted to know what proportion of cancer deaths can be attributed to energy related technologies or to environmental factors. Both undoubtedly contribute to some extent. Such information is hard to obtain because cancers are caused by multiple factors working together and the contributions of individual factors are difficult to assess. Even if energy related and environmental factors are found to be minor causes of cancer, however, they will still be significant because the cancer problem is huge and because unnecessary exposures can be reduced or avoided, as has been shown for radiation.

Economic Cost of Cancer

2. You state that "in addition to the untold suffering, the economic cost of cancer is an estimated 50 billion dollars in 1983."

   A. If the DOE support for cancer research, which is about $41 million in 1983, were increased, could it result in a significant decrease in suffering as well as in the cost?

   ANSWER: Yes. The cancer research program conducted by the Department of Energy is designed to prevent cancer. To the extent that the program succeeds, both the suffering and the costs of cancer will be avoided. A ten-fold increase in support for cancer research from the Department of Energy could be readily utilized by the existing national resources of scientists and facilities. I confidently predict that that investment would be returned many-fold from the reduced costs of hospitalization and from prolonged employment. The return from reduced suffering and from the fear of cancer is incalcuable but enormous.

   B. Can the DOE budget and research program in cancer be increased without overlapping with the research program of the National Cancer Institute? Would this also be true of the research programs at the Oak Ridge National Laboratory?

   ANSWER: Yes, the Department of Energy budget for cancer research can be greatly increased without overlap with the National Cancer Institute. The cancer research programs of the Department of Energy and of the National Cancer Institute are coordinated by both agencies so that they are complementary. In radiation carcinogenesis, for example, the focus of the National Cancer Institute is on improved methods for treating cancer patients with radiation and on the late effects of radiation on people who have received therapeutic doses of radiation for various diseases. The Department of Energy deals with the effects of low doses of radiation in the workplace, acute exposure to radiation as in the Japanese survivors of atom bomb blasts, and the medical uses of radioactive materials taken internally. In chemical carcinogenesis, too, the focus of the two agencies is different. The National Cancer Institute tends to concentrate on the effects of single chemicals while the Department of Energy (because of its interests in alternate energy sources) must deal with complex chemical mixtures. The research programs at the Oak Ridge National Laboratory that are supported by the National Cancer Institute are all reviewed and approved by the Department of Energy for priority, need, and relevance to prevent unnecessary overlap. The joint Department of Energy-National Cancer Institute cancer research program at the Oak Ridge National Laboratory has been in existence for 20 years.

Skin Cancer Studies

3. Recent experiments conducted at Oak Ridge National Laboratory showed that synthetic fuels caused skin cancer.

A. What is the current status of that research program?

ANSWER: The Oak Ridge National Laboratory, in conjunction with the activities sponsored by the Office of Health and Environmental Research at other Department of Energy National Laboratories, has demonstrated that coal-derived liquids cause cancer when applied to the skin of mice. Many of the carcinogenic ingredients have been identified. We have discovered that the carcinogenic activity can be abolished by physical separation methods or by chemical methods (treatment with hydrogen). In progress are comparative studies of the extent of absorption and metabolism in the skins of animals and humans. Because of budget constraints we have had to defer research on the effectiveness of washing and of barrier creams to prevent skin cancer. Urgently needed studies on the interaction of sunlight (a known skin carcinogen) and synfuel materials in the induction of skin cancer have also had to be deferred. Moreover, two of three groups of scientists working on skin cancer at the Oak Ridge National Laboratory have left the Laboratory this year as a direct consequence of reductions in staffing made necessary by declining budgets. Budget restrictions have prevented replacing them and in this particular area ORNL has lost its internationally recognized capability to investigate the cancer promoting effects of substances that by themselves do not produce cancer. We have demonstrated also that ingredients of synfuels reach the inner organs of the body after application to the skin. Toxic effects on the kidney, brain, and unborn fetus have been demonstrated but the possibility of cancer formation in internal organs awaits future long-term research that is as yet unfunded.

B. What additional cancer related research programs are underway at the Laboratory?

ANSWER: The cancer research programs at the Oak Ridge National Laboratory deal with the potential carcinogenicity of energy-related substances. Particular emphasis is placed on understanding the mechanisms of the cancer process so that a rational basis is obtained for preventing the disease from beginning or from progressing to an irreversible and fatal state. In radiation carcinogenesis, for example, low dose response experiments with neutrons, heavy ions, and ultraviolet light are in progress in animals to provide data for risk estimates so that radiation protection standards can be established for humans. We have learned, for example, that divided doses of neutron radiation are more carcinogenic than single doses (in contrast with x-radiation), that dose-response curves for neutron-induced cancer are not linear, and that currently used dose-response models do not estimate accurrately the risk at low doses for nearly all cancers. Since human protection depends on extrapolation from animal studies, these findings are essential for the prevention of cancer without imposing unnecessary and very expensive restrictions on human exposure. Because the Oak Ridge National Laboratory has a very strong capability in genetics research and in molecular biology, much of the cancer research capitalizes on the advances in those fields. Included are studies on the role of transposition of genes on cancer induction, the repair of damaged genetic material, regulation of cancer gene expression, alterations in chromosomes, inherited genetic restriction of cancer induction, genetic evidence for pre-cancerous changes and genetic influences on carcinogen metabolism. One of the many uses of such research is to determine whether there are subpopulations of workers with genetically determined susceptibility or resistance to cancer.

Impact of the FY 1984 Budget Request

4. You state that budget cuts have caused a 41% reduction in biology staff the last three years, with projections for an additional 16% reduction in 1984.

   A. What impact will this have on cancer research at the Oak Ridge National Laboratory?

   B. How will the proposed budget cuts affect the long-term research program under way at Oak Ridge?

ANSWER: The impact of the 41% reduction in staff has been far greater than a 41% reduction in the scope of activities. The sizeable reductions in staff have created uncertainties among the entire remaining staff concerning whether each of them might lose employment in a subsequent year. Accordingly, many of the scientists and their trained technicians are seeking positions elsewhere. Not all will stay in cancer research or even in science. Another budget cut in FY 1984 will be interpreted by the staff as a clear signal that the Government is not interested in continuing biomedical research in the Department of

Energy's National Laboratories. In my judgment, cancer research at the Oak Ridge National Laboratory will then become impossible because the brain drain will be irreversible. The full-time doctoral staff in cancer research at the Oak Ridge National Laboratory has already been reduced from 27 to 14 in three years. In radiation carcinogenesis, there is only one scientist under 55 years of age now working at the Oak Ridge National Laboratory.

C. If Oak Ridge and DOE cut research in cancer programs, who will continue this important program?

ANSWER: No one. Other federal agencies have neither the mandate nor the funds to fulfill the missions of the Department of Energy.

INTRA-LABORATORY CORRESPONDENCE

OAK RIDGE NATIONAL LABORATORY

June 8, 1983

To: R. A. Griesemer

From: J. B. Storer JBS

Subject: Comparison of AEC's Biomedical Research Budget in 1969 and OHER's FY-84 Request

In 1969 the Division of Biology and Medicine had a total budget of approximately $100 million. OHER's 1984 request is for $210 million. In 1969 we did not support "Environment, Safety and Health". This was in a separate division (Division of Occupational Safety). We also did not support "CO_2 and climate" and "risk analysis". We had fewer than 100 employees.

When we deduct the areas of work we did not support we find OHER's request for 1984 is $158.2 million compared to our $100 million. I don't know the inflation factor for the past 15 years. It must be at least a factor of 2. (An annual inflation rate of 4.6% gives a factor of two.) A more realistic inflation rate is probably 7%. No matter how you figure it we have lost considerable ground in terms of constant dollars during a period when OHER's responsibilities have increased.

JBS:cr

P.S. at a 7% annual rate of inflation, OHER would need $286 million rather than $158 million to support the programs at the same level as our $100 million in 1969.